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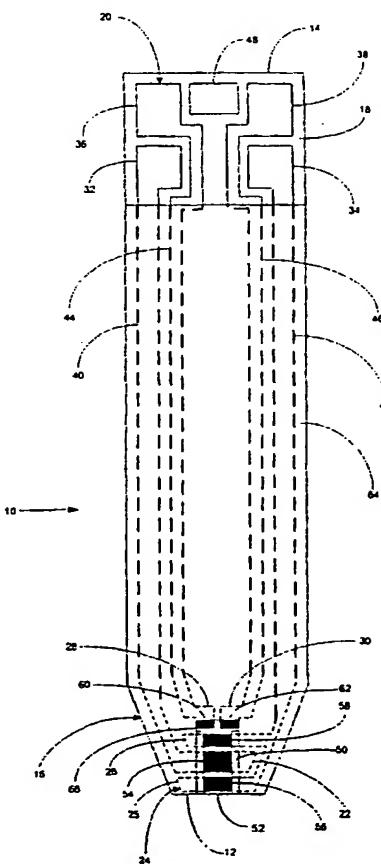
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(54) Title: SYSTEMS AND METHODS FOR BLOOD GLUCOSE SENSING



(57) Abstract: A system for measuring a glucose level in a blood sample includes a test strip (10) and a meter. The test strip (10) includes a sample chamber, a working electrode (22), a counter electrode (24), fill-detect electrodes (28, 30), and an auto-on conductor (48). A reagent layer is disposed in the sample chamber. The auto-on conductor (48) causes the meter to wake up and perform a test strip sequence when the test strip (10) is inserted in the meter. The meter uses the working and counter electrodes (22, 24) to initially detect the blood sample in the sample chamber and uses the fill-detect electrodes (28, 30) to check that the blood sample has mixed with the reagent layer. The meter applies an assay voltage between the working and counter electrodes (22, 24) and measures the resulting current. The meter calculates the glucose level based on the measured current and calibration data saved in memory from a removable data storage device associated with the test strip (10).

WO 03/091717 A1

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SYSTEMS AND METHODS FOR BLOOD GLUCOSE SENSING

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/375,017, filed April 25, 2002, U.S. Provisional Patent Application Serial No. 60/375,019, filed April 25, 2002, U.S. Provisional Patent Application Serial No. 60/375,020, filed April 25, 2002, and U.S. Provisional Patent Application Serial No. 10 60/375,054, filed April 25, 2002, all of which are fully incorporated herein by reference. This application is also a continuation-in-part of U.S. Application Serial No. 10/286,648, filed November 1, 2002, which is fully incorporated herein by reference.

BACKGROUND

15 1. **Field of the Invention**
The present invention relates to electrochemical sensors and, more particularly, to systems and methods for sensing blood glucose levels electrochemically.

2. **Description of Related Art**
Many people, such as diabetics, have a need to monitor their blood glucose levels
20 on a daily basis. A number of systems that allow people to conveniently monitor their blood glucose levels are available. Such systems typically include a test strip where the user applies a blood sample and a meter that "reads" the test strip to determine the glucose level in the blood sample.

Among the various technologies available for measuring blood glucose levels,
25 electrochemical technologies are particularly desirable because only a very small blood sample may be needed to perform the measurement. In electrochemical-based systems,

the test strip typically includes a sample chamber that contains reagents, such as glucose oxidase and a mediator, and electrodes. When the user applies a blood sample to the sample chamber, the reagents react with the glucose, and the meter applies a voltage to the electrodes to cause a redox reaction. The meter measures the resulting current and calculates the glucose level based on the current.

It should be emphasized that accurate measurements of blood glucose levels may be critical to the long-term health of many users. As a result, there is a need for a high level of reliability in the meters and test strips used to measure blood glucose levels. However, as sample sizes become smaller, the dimensions of the sample chamber and electrodes in the test strip also become smaller. This, in turn, may make test strips become more sensitive to smaller manufacturing defects and to damage from subsequent handling.

Accordingly, there is a need to provide blood glucose measuring systems and methods with features for measuring blood glucose levels conveniently and reliably.

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SUMMARY

In a first principal aspect, the present invention provides a test strip for testing a blood sample. The test strip comprises a sample chamber for the blood sample, at least four electrodes for measuring at least one electrical characteristic of the blood sample in the sample chamber, a plurality of electrical contacts electrically connected to the at least four electrodes, and at least one auto-on electrical contact electrically isolated from the at least four electrodes. The at least four electrodes include a working electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode.

In a second principal aspect, the present invention provides a method of making a plurality of test strips. In accordance with the method, a plurality of test strip structures

are formed on one sheet, and the test strip structures are separated into test strips. Each of the test strip structures includes a sample chamber, a plurality of electrodes (including a working electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode), a plurality of electrical contacts electrically connected to the electrodes, and at least one auto-on electrical contact electrically isolated from the plurality of electrodes.

In a third principal aspect, the present invention provides a method of using a test strip to test a blood sample. The test strip includes a sample chamber, a working electrode, a counter electrode, a pair of fill-detect electrodes, and an auto-on conductor. In accordance with the method, the test strip is inserted into a meter that is in a sleep mode. The meter detects an auto-on current through the auto-on conductor and responsively enters an active mode. The blood sample is applied to the sample chamber. The meter detects the blood sample in the sample chamber by applying a fill-detect voltage between the fill-detect electrodes and measuring a fill-detect current flowing between the fill-detect electrodes. The meter applies an assay voltage between the working and counter electrodes and makes at least one measurement of the resulting current. The meter determines a test result from the at least one current measurement.

In a fourth principal aspect, the present invention provides a method of strip identification. A strip that includes an auto-on conductor is inserted into a meter that is in a sleep mode. The meter detects the strip by detecting a current flow through the auto-on conductor, and responsively enters an active mode. The meter measures a voltage drop across the auto-on conductor and identifies the strip as either a test strip or a check strip based on the voltage drop. If the strip is a test strip, the meter performs a test strip sequence. If the strip is a check strip, the meter performs a check strip sequence.

In a fifth principal aspect, the present invention provides a removable data storage device for a meter that uses test strips to measure glucose levels in blood samples. The

removable data storage device comprises a carrier, a circuit board mounted to the carrier, and a memory mounted to the circuit board. The carrier has a proximal end and a distal end and is keyed for inserting the distal end into the meter in a preferred orientation. The circuit board includes a plurality of electrical contacts for electrically connecting to the meter. The plurality of electrical contacts includes a ground contact and a voltage supply contact. The ground contact extends closer to the distal end than the voltage supply contact. The memory stores data for use by the meter, including calibration coefficients for a plurality of test strips. The memory is electrically connected to the plurality of electrical contacts on the circuit board. When the removable data storage device is inserted into the meter in the preferred orientation, the ground contact becomes electrically connected to the meter before the voltage supply contact.

In a sixth principal aspect, the present invention provides a meter for use in combination with a test strip. The test strip includes a working electrode, a counter electrode, a pair of fill-detect electrodes, and an auto-on conductor. The meter comprises a strip connector for receiving the test strip, a processor, a memory, a plurality of machine instructions stored in the memory and executable by the processor for performing a test strip sequence, and a data acquisition system controlled by the processor. When the test strip is inserted in the strip connector, the data acquisition system applies at least a first voltage between the working and counter electrodes and measures any resulting current flowing between the working and counter electrodes, applies at least a second voltage between the fill-detect electrodes and measures any resulting current flowing between the fill-detect electrodes, and measures a voltage drop across the auto-on conductor. The data acquisition system includes at least one digital-to-analog converter and at least one analog-to-digital converter.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a top plan view of a test strip, in accordance with a first exemplary embodiment of the present invention.

5 Figure 2 is a top plan view of the test strip of Figure 1, with the cover, adhesive layer, and reagent layer cut away, in accordance with a first exemplary embodiment of the present invention.

Figure 3 is a cross-sectional view of the test strip of Figure 1, taken along line 3—3, in accordance with a first exemplary embodiment of the present invention.

10 Figure 4 is a top plan view of a test strip, in accordance with a second exemplary embodiment of the present invention.

Figure 5 is a top plan view of a test strip, in accordance with a third exemplary embodiment of the present invention.

15 Figure 6 is a top schematic view of an array of test strip structures, which may be separated into a plurality of test strips of the type shown in Figures 1-3, in accordance with an exemplary embodiment of the present invention.

Figure 7 is top plan view of an intermediate stage in the formation of one of the test strip structures of Figure 6, in accordance with an exemplary embodiment of the present invention.

20 Figure 8 is top plan view of an intermediate stage in the formation of one of the test strip structures of Figure 6, in accordance with an exemplary embodiment of the present invention.

Figure 9 is top plan view of an intermediate stage in the formation of one of the test strip structures of Figure 6, in accordance with an exemplary embodiment of the present invention.

Figure 10 is top plan view of an intermediate stage in the formation of one of the test strip structures of Figure 6, in accordance with an exemplary embodiment of the present invention.

5 Figure 11 is top plan view of one of the test strip structures of Figure 6, in accordance with an exemplary embodiment of the present invention.

Figure 12 is a perspective view of a meter, in accordance with an exemplary embodiment of the present invention.

10 Figure 13 is a perspective view of the meter of Figure 12, with a removable data storage device inserted in it, in accordance with an exemplary embodiment of the present invention.

Figure 14 is a perspective view of a strip connector in the meter of Figure 12, in accordance with an exemplary embodiment of the present invention.

15 Figure 15 is an exploded perspective view of the removable data storage device of Figure 13, in accordance with an exemplary embodiment of the present invention.

Figure 16 is a flow chart illustrating a method of using a test strip or a check strip, in accordance with an exemplary embodiment of the present invention.

Figure 17 is a flow chart illustrating a method of using a check strip, in accordance with an exemplary embodiment of the present invention.

20 Figure 18 is a flow chart illustrating a method of using a test strip, in accordance with an exemplary embodiment of the present invention.

Figure 19 is a flow chart illustrating a method of using a test strip, in accordance with an exemplary embodiment of the present invention.

Figure 20 is a simplified schematic diagram of the electronics of the meter of Figure 12, in accordance with an exemplary embodiment of the present invention.

Figure 21 is a simplified schematic diagram of the electrical connections between the meter of Figure 12 and the electrodes of the test strip of Figure 1, in accordance with an exemplary embodiment of the present invention.

5 Figure 22 is a simplified schematic diagram of the electrical connections between the meter of Figure 12 and the auto-on conductor of the test strip of Figure 1, in accordance with an exemplary embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with a preferred embodiment, a system for measuring a glucose 10 level in a blood sample includes a test strip and a meter. The system may also include a removable data storage device associated with a lot of test strips. The removable data storage device stores data for use by the meter, such as calibration coefficients for test strips from that lot. The system may also include a check strip that the user may insert into the meter to check that the meter is functioning properly.

15 The test strip includes a sample chamber for receiving the blood sample. The sample chamber has a first opening in the proximal end of the test strip and a second opening for venting the sample chamber. The sample chamber may be dimensioned so as to be able to draw the blood sample in through the first opening, and to hold the blood sample in the sample chamber, by capillary action. The test strip may include a tapered 20 section that is narrowest at the proximal end, in order to make it easier for the user to locate the first opening and apply the blood sample.

A working electrode, a counter electrode, a fill-detect electrode, and a fill-detect 25 anode are disposed in the sample chamber. A reagent layer is disposed in the sample chamber and preferably covers at least the working electrode. The reagent layer may include an enzyme, such as glucose oxidase, and a mediator, such as potassium

ferricyanide. The test strip has, near its distal end, a plurality of electrical contacts that are electrically connected to the electrodes via conductive traces. The test strip also has near its distal end an auto-on conductor, which may be electrically isolated from the electrodes.

5 The meter may be battery powered and may stay in a low-power sleep mode when not in use in order to save power. When the test strip is inserted into the meter, the electrical contacts on the test strip contact corresponding electrical contacts in the meter. In addition, the auto-on conductor bridges a pair of electrical contacts in the meter, causing a current to flow through the auto-on conductor. The current flow through the 10 auto-on conductor causes the meter to wake up and enter an active mode. The meter also measures the voltage drop across the auto-on conductor and identifies the inserted strip as either a test strip or a check strip based on the voltage drop. If the meter detects a check strip, it performs a check strip sequence. If the meter detects a test strip, it performs a test strip sequence.

15 In the test strip sequence, the meter validates the working electrode, counter electrode, and fill-detect electrodes by confirming that there are no low-impedance paths between any of these electrodes. If the electrodes are valid, the meter indicates to the user that sample may be applied to the test strip. The meter then applies a drop-detect voltage between the working and counter electrodes and detects the blood sample by detecting a 20 current flow between the working and counter electrodes (i.e., a current flow through the blood sample as it bridges the working and counter electrodes). To detect that adequate sample is present in the sample chamber and that the blood sample has traversed the reagent layer and mixed with the chemical constituents in the reagent layer, the meter applies a fill-detect voltage between the fill-detect electrodes and measures any resulting 25 current flowing between the fill-detect electrodes. If this resulting current reaches a

sufficient level within a predetermined period of time, the meter indicates to the user that adequate sample is present and has mixed with the reagent layer.

The meter waits for an incubation period of time after initially detecting the blood sample, to allow the blood sample to react with the reagent layer. Then, during a measurement period, the meter applies an assay voltage between the working and counter electrodes and takes one or more measurements of the resulting current flowing between the working and counter electrodes. The assay voltage is near the redox potential of the chemistry in the reagent layer, and the resulting current is related to the glucose level in the blood sample. The meter calculates the glucose level based on the measured current and on calibration data that the meter previously downloaded from the removable data storage device associated with the test strip and stored in the meter's memory. The meter then displays the calculated glucose level to the user.

1. Test strip configuration

With reference to the drawings, Figures 1, 2, and 3 show a test strip 10, in accordance with an exemplary embodiment of the present invention. Test strip 10 preferably takes the form of a generally flat strip that extends from a proximal end 12 to a distal end 14. Preferably, test strip 10 is sized for easy handling. For example, test strip 10 may be about 1 3/8 inches along its length (i.e., from proximal end 12 to distal end 14) and about 5/16 inches wide. However, proximal end 12 may be narrower than distal end 14. Thus, test strip 10 may include a tapered section 16, in which the full width of test strip 10 tapers down to proximal end 12, making proximal end 12 narrower than distal end 14. As described in more detail below, the user applies the blood sample to an opening in proximal end 12 of test strip 10. Thus, providing tapered section 16 in test strip 10, and making proximal end 12 narrower than distal end 14, may help the user to

locate the opening where the blood sample is to be applied and may make it easier for the user to successfully apply the blood sample to test strip 10.

As best shown in Figure 3, test strip 10 may have a generally layered construction. Working upward from the lowest layer, test strip 10 may include a base layer 18 extending along the entire length of test strip 10. Base layer 18 is preferably composed of an electrically insulating material and has a thickness sufficient to provide structural support to test strip 10. For example, base layer 18 may be polyester that is about 0.014 inches thick.

Disposed on base layer 18 is a conductive pattern 20. Conductive pattern 20 includes a plurality of electrodes disposed on base layer 18 near proximal end 12, a plurality of electrical contacts disposed on base layer 18 near distal end 14, and a plurality of conductive traces electrically connecting the electrodes to the electrical contacts. In a preferred embodiment, the plurality of electrodes includes a working electrode 22, a counter electrode 24, which may include a first section 25 and a second section 26, a fill-detect anode 28, and a fill-detect cathode 30. Correspondingly, the electrical contacts may include a working electrode contact 32, a counter electrode contact 34, a fill-detect anode contact 36, and a fill-detect cathode contact 38. The conductive traces may include a working electrode trace 40, electrically connecting working electrode 22 to working electrode contact 32, a counter electrode trace 42, electrically connecting counter electrode 24 to counter electrode contact 34, a fill-detect anode trace 44 electrically connecting fill-detect anode 28 to fill-detect contact 36, and a fill-detect cathode trace 46 electrically connecting fill-detect cathode 30 to fill-detect cathode contact 38. In a preferred embodiment, conductive pattern 20 also includes an auto-on conductor 48 disposed on base layer 18 near distal end 14.

A dielectric layer 50 may also be disposed on base layer 18, so as to cover portions of conductive pattern 20. Preferably, dielectric layer 50 is a thin layer (e.g., about 0.0005 inches thick) and is composed of an electrically insulating material, such as silicones, acrylics, or mixtures thereof. Preferably, dielectric layer 50 is also hydrophilic.

5 Dielectric layer 50 may cover portions of working electrode 22, counter electrode 24, fill-detect anode 28, fill-detect cathode 30, and conductive traces 40-46, but preferably does not cover electrical contacts 32-38 or auto-on conductor 48. For example, dielectric layer 50 may cover substantially all of base layer 18, and the portions of conductive pattern 20 thereon, from a line just proximal of contacts 32 and 34 all the way to proximal end 12, except for a slot 52 extending from proximal end 12. In this way, slot 52 may define an exposed portion 54 of working electrode 22, exposed portions 56 and 58 of sections 25 and 26 of counter electrode 24, an exposed portion 60 of fill-detect anode 28, and an exposed portion 62 of fill-detect cathode 30. As shown in Figure 2, slot 52 may have different widths in different sections, which may make exposed portions 60 and 62 of fill-detect electrodes 28 and 30 wider than exposed portions 54, 56, and 58 of working electrode 22 and counter electrode sections 25 and 26.

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The next layer in test strip 10 may be a dielectric spacer layer 64 disposed on dielectric layer 50. Dielectric spacer layer 64 is composed of an electrically insulating material, such as polyester. Dielectric spacer layer 64 may have a length and width similar to that of dielectric layer 50 but may be substantially thicker, e.g., about 0.005 inches thick. In addition, spacer 64 may include a slot 66 that is substantially aligned with slot 52. Thus, slot 66 may extend from a proximal end 68, aligned with proximal end 12, back to a distal end 70, such that exposed portions 54 – 62 of working electrode 22, counter electrode 24, fill-detect anode 28, and fill-detect cathode 30 are located in slot 20

25 66.

A cover 72, having a proximal end 74 and a distal end 76, may be attached to dielectric spacer layer 64 via an adhesive layer 78. Cover 72 is composed of an electrically insulating material, such as polyester, and may have a thickness of about 0.004 inches. Preferably, cover 72 is transparent.

5 Adhesive layer 78 may include a polyacrylic or other adhesive and have a thickness of about 0.0005 inches. Adhesive layer 78 may consist of a first section 80 and a second section 82 disposed on spacer 64 on opposite sides of slot 66. A break 84 in adhesive layer 78 between sections 80 and 82 extends from distal end 70 of slot 66 to an opening 86. Cover 72 may be disposed on adhesive layer 78 such that its proximal end 74 is aligned with proximal end 12 and its distal end 76 is aligned with opening 86. In
10 this way, cover 72 covers slot 66 and break 84.

Slot 66, together with base layer 18 and cover 72, defines a sample chamber 88 in test strip 10 for receiving a blood sample for measurement. Proximal end 68 of slot 66 defines a first opening in sample chamber 88, through which the blood sample is introduced into sample chamber 88. At distal end 70 of slot 66, break 84 defines a second opening in sample chamber 88, for venting sample chamber 88 as sample enters sample chamber 88. Slot 66 is dimensioned such that a blood sample applied to its proximal end 68 is drawn into and held in sample chamber 88 by capillary action, with break 84 venting sample chamber 88 through opening 86, as the blood sample enters. Moreover,
15 slot 66 is dimensioned so that the blood sample that enters sample chamber 88 by capillary action is about 1 microliter or less. For example, slot 66 may have a length (i.e., from proximal end 68 to distal end 70) of about .140 inches, a width of about .060 inches, and a height (which may be substantially defined by the thickness of dielectric spacer layer 64) of about .005 inches. Other dimensions could be used, however.
20

A reagent layer 90 is disposed in sample chamber 88. Preferably, reagent layer 90 covers at least exposed portion 54 of working electrode 22. Most preferably, reagent layer 90 also at least touches exposed portions 56 and 58 of counter electrode 24. Reagent layer 90 includes chemical constituents to enable the level of glucose in the blood sample to be determined electrochemically. Thus, reagent layer 90 may include an enzyme specific for glucose, such as glucose oxidase, and a mediator, such as potassium ferricyanide. Reagent layer 90 may also include other components, such as buffering materials (e.g., potassium phosphate), polymeric binders (e.g., hydroxypropyl-methylcellulose, sodium alginate, microcrystalline cellulose, polyethylene oxide, hydroxyethylcellulose, and/or polyvinyl alcohol), and surfactants (e.g., Triton X-100 or 10 Surfynol 485).

With these chemical constituents, reagent layer 90 reacts with glucose in the blood sample in the following way. The glucose oxidase initiates a reaction that oxidizes the glucose to gluconic acid and reduces the ferricyanide to ferrocyanide. When an appropriate voltage is applied to working electrode 22, relative to counter electrode 24, 15 the ferrocyanide is oxidized to ferricyanide, thereby generating a current that is related to the glucose concentration in the blood sample.

As best shown in Figure 3, the arrangement of the various layers in test strip 10 may result in test strip 10 having different thicknesses in different sections. In particular, 20 among the layers above base layer 18, much of the thickness of test strip 10 may come from the thickness of spacer 64. Thus, the edge of spacer 64 that is closest to distal end 14 may define a shoulder 92 in test strip 10. Shoulder 92 may define a thin section 94 of test strip 10, extending between shoulder 92 and distal end 14, and a thick section 96, extending between shoulder 92 and proximal end 12. The elements of test strip 10 used 25 to electrically connect it to the meter, namely, electrical contacts 32 – 38 and auto-on

conductor 48, may all be located in thin section 94. Accordingly, the connector in the meter may be sized so as to be able to receive thin section 94 but not thick section 96, as described in more detail below. This may beneficially cue the user to insert the correct end, i.e., distal end 14 in thin section 94, and may prevent the user from inserting the wrong end, i.e., proximal end 12 in thick section 96, into the meter.

Although Figures 1 – 3 illustrate a preferred configuration of test strip 10, other configurations could be used. For example, in the configuration shown in Figures 1 – 3, counter electrode 24 is made up two sections, a first section 25 that is on the proximal side of working electrode 22 and a second section 26 that is on the distal side of working electrode 22. Moreover, the combined area of the exposed portions 56 and 58 of counter electrode 24 is preferably greater than the area of the exposed portion 54 of working electrode 22. In this configuration, counter electrode 24 effectively surrounds working electrode 22, which beneficially shields working electrode 22 electrically. In other configurations, however, counter electrode 24 may have only one section, such as first section 25.

Different arrangements of fill-detect electrodes 28 and 30 may also be used. In the configuration shown in Figures 1 – 3, fill-detect electrodes 28 and 30 are in a side-by-side arrangement. Alternatively, fill-detect electrodes 28 and 30 may be in a sequential arrangement, whereby, as the sample flows through sample chamber 88 toward distal end 70, the sample contacts one of the fill-detect electrodes first (either the anode or the cathode) and then contacts the other fill-detect electrode. In addition, although exposed portions 60 and 62 of fill-detect electrodes 28 and 30 are wider than exposed portions 54, 56, and 58 of working electrode 22 and counter electrode sections 25 and 26 in the embodiment shown in Figure 2, they may have the same or a narrower width in other embodiments.

However they are arranged relative to each other, it is preferable for fill-detect electrodes 28 and 30 to be located on the distal side of reagent layer 90. In this way, as the sample flows through sample chamber 88 toward distal end 70, the sample will have traversed reagent layer 90 by the time it reaches fill-detect electrodes 28 and 30. This arrangement beneficially allows the fill-detect electrodes 28 and 30 to detect not only whether sufficient blood sample is present in sample chamber 88 but also to detect whether the blood sample has become sufficiently mixed with the chemical constituents of reagent layer 90. Thus, if reagent layer 90 covers working electrode 22, as is preferable, then it is preferable to locate fill-detect electrodes 28 and 30 on the distal side of working electrode 22, as in the configuration shown in Figure 1 – 3. Other configurations may be used, however.

Different configurations of the sample chamber in the test strip are also possible. For example, Figure 4 shows an alternate embodiment, test strip 100, in which the sample chamber is vented without the use of a break in an adhesive layer. In test strip 100, spacer 64 includes a vented slot 102 that defines the sample chamber. Slot 102 includes a wide section 104, which may have a relatively uniform width, a tapered section 106, which may have a rounded shape, and a narrow section 108, which may also have a rounded shape. The exposed portions of the working and counter electrodes may be located in wide section 104 and the proximal end of tapered section 106, and the exposed portions of the fill-detect electrodes may be located in the distal end of tapered section 106. Cover 72 is attached to spacer 64 (e.g., using an adhesive) so as to cover slot 102 except for a distal end of narrow section 108. In this way, narrow section 108 may vent the sample chamber defined by slot 102. In addition, the rounded shape of tapered section 106 may allow the sample to flow through the sample chamber more smoothly and uniformly.

A vented slot need not have a rounded shape, however. For example, Figure 5 shows another alternate embodiment, test strip 110, in which the sample chamber is also vented without the use of a break in an adhesive layer. In test strip 110, spacer 64 includes a vented slot 112 that defines the sample chamber. Slot 112 includes a wide section 114, which may have a relatively uniform width, and a narrow section 116, which may also have a relatively uniform width. The exposed portions of the working, counter, and fill-detect electrodes may all be located in wide section 114, with the exposed portions of the fill-detect electrodes located at the distal end of wide section 114. Cover 72 is attached to spacer 64 (e.g., using an adhesive) so as to cover slot 112, except for a distal end of narrow section 116. In this way, narrow section 116 may vent the sample chamber defined by slot 112.

Other configurations of test strip, for example, with other configurations of electrodes and/or sample chamber may also be used.

2. Method of manufacturing test strips

Figures 6 through 11 illustrate an exemplary method of manufacturing test strips. Although these figures shows steps for manufacturing test strip 10, as shown in Figures 1 – 3, it is to be understood that similar steps may be used to manufacture test strips having other configurations, such as test strip 100 shown in Figure 4 and/or test strip 110 shown in Figure 5.

With reference to Figure 6, a plurality of test strips 10 may be mass-produced by forming an integrated structure 120 that includes a plurality of test strip structures 122 all on one sheet. The test strip structures 122 may be arranged in an array that includes a plurality of rows 124 (e.g., six rows), with each row 124 including a plurality of test strip structures 122 (e.g., fifty test strip structures in each row). The plurality of test strips 10 may then be formed by separating the test strip structures 122 from each other. In a

preferred separation process, each row 124 of test strip structures 122 is first punched out of integrated structure 120. This punching process may provide some of the outer shape of the test strips 10. For example, the tapered shape of tapered sections 16 of the test strips 10 may be formed in this punching process. Next, a slitting process may be used to 5 separate the test strip structures 122 in each row 124 into individual test strips 10.

Figures 7 through 11 show only one test strip structure (either partially or completely fabricated), in order to illustrate various steps in a preferred method for forming the test strip structures 122. In this preferred approach, the test strip structures 122 in integrated structure 120 are all formed on a sheet of material that serves as base 10 layer 18 in the finished test strips 10. The other components in the finished test strips 10 are then built up layer-by-layer on top of base layer 18 to form the test strip structures 122. In each of Figures 7 through 11, the outer shape of the test strip 10 that would be formed in the overall manufacturing process is shown as a dotted line.

As shown in Figure 7, the manufacturing process may begin by forming, for each 15 test strip structure, a first conductive pattern 130 on base layer 18. First conductive pattern 130 may include electrical contacts 32-38, conductive traces 40-42, and auto-on conductor 48. First conductive pattern 130 may be formed by screen-printing a first conductive ink onto base layer 18. The first conductive ink may be provided as a viscous liquid that includes particles of a conductive material, such as metallic silver. For 20 example, a preferred first conductive ink has a composition of about 30 – 60 weight % metallic silver, about 5 – 10 weight % lamp black, about 30 – 60 weight % dipropylene glycol monomethyl ether, and other components, and is available from E.I. DuPont de Nemours & Co., Wilmington, Delaware, as “Membrane Switch Composition 5524.”

As shown in Figure 8, a second conductive pattern 132 may then be formed on 25 base layer 18. Second conductive pattern 132 may include working electrode 22, first

section 25 and second section 26 of counter electrode 24, fill-detect anode 28, and fill-detect cathode 30. Second conductive pattern 132 may be formed by screen-printing a second conductive ink onto base layer 18. The second conductive ink may be provided as a viscous liquid that includes particles of a conductive material, such as graphite. The 5 second conductive ink may have a different composition than the first conductive ink. In particular, the second conductive ink is preferably substantially of free of materials, such as silver, that can interfere with the chemistry of reagent layer 90. A preferred second conductive ink has a composition of about 10 – 20 weight % graphite, about 5 – 10 weight % lamp black, greater than 60 weight % ethylene glycol diacetate, and about 5 – 10 weight % polymer, and is available from E.I. DuPont de Nemours & Co., Wilmington, Delaware, as “E100735-111.”

As shown in Figure 9, dielectric layer 50 may then be formed on base layer 18 so as to cover portions of first conductive pattern 130 and second conductive pattern 132. As shown in Figure 9, dielectric layer 50 may extend beyond the outline of a finished test strip 10 so as to cover multiple test strip structures being formed on base layer 18. Also 15 as shown in Figure 9, dielectric layer 50 may include a slot 134 that defines exposed portions 54, 56, 58, 60, and 62 of working electrode 22, first counter electrode section 25, second counter electrode section 26, fill-detect anode portion 28, and fill-detect cathode portion 30. Slot 52 in test strip 10 corresponds to the part of slot 134 that remains in test strip 10 after the test strip structures are separated into test strips. In this regard, slot 134 20 may include a wide section 135 to allow the portions of fill-detect electrodes 28 and 30 left exposed by layer 50 to be wider than the portions of working electrode 22 and counter electrode 24 left exposed by layer 50.

In a preferred approach, dielectric layer 50 is hydrophilic and is applied by screen-printing a dielectric material. A preferred dielectric material comprises a mixture of 25

silicone and acrylic compounds, such as the "Membrane Switch Composition 5018" available from E.I. DuPont de Nemours & Co., Wilmington, Delaware. Other materials could be used, however.

In the next step, dielectric spacer layer 64 may be applied to dielectric layer 50, as illustrated in Figure 10. Spacer 64 may be applied to dielectric layer 50 in a number of different ways. In an exemplary approach, spacer 64 is provided as a sheet large enough and appropriately shaped to cover multiple test strip structures. In this approach, the underside of spacer 64 may be coated with an adhesive to facilitate attachment to dielectric layer 50 and base layer 18. Portions of the upper surface of spacer 64 may also be coated with an adhesive in order to provide adhesive layer 78 in each of the test strips 10. Various slots may be cut into or punched out of spacer 64 to shape it before spacer layer 64 is applied to dielectric layer 50. For example, as shown in Figure 10, spacer 64 may have a slot 136 for each test strip structure and a slot 138 that extends over multiple test strip structures. In addition, spacer 64 may include adhesive sections 140 and 142, with break 84 therebetween, for each test strip structure being formed. Spacer 64 is then positioned over base layer 18, as shown in Figure 10, and laminated to base layer 18 and dielectric layer 50. When spacer 64 is appropriately positioned on base layer 18, exposed electrode portions 54 – 62 are accessible through slot 136. Thus, slot 66 in test strip 10 corresponds to that part of slot 136 that remains in test strip 10 after the test strip structures are separated into test strips. Similarly, slot 138 in spacer 64 leaves contacts 32 – 38 and auto-on conductor 48 exposed after lamination.

Alternatively, spacer 64 could be applied in other ways. For example, spacer 64 may be injection molded onto base layer 18 and dielectric 50. Spacer 64 could also be built up on dielectric layer 50 by screen-printing successive layers of a dielectric material to an appropriate thickness, e.g., about 0.005 inches. A preferred dielectric material

comprises a mixture of silicone and acrylic compounds, such as the "Membrane Switch Composition 5018" available from E.I. DuPont de Nemours & Co., Wilmington, Delaware. Other materials could be used, however.

Reagent layer 90 may then be applied to each test strip structure. In a preferred approach, reagent layer 90 is applied by micropipetting an aqueous composition onto exposed portion 54 of working electrode 22 and letting it dry to form reagent layer 90. A preferred aqueous composition has a pH of about 6 and contains 2 weight % polyvinyl alcohol, 0.1 M potassium phosphate, 0.05 weight % Triton X-100, 0.15 M potassium ferricyanide, 0.7 % hydroxyethylcellulose (such as NATROSOL®), and about 2500 units of glucose oxidase per mL. Alternatively, other methods, such as screen-printing, may be used to apply the composition used to form reagent layer 90.

A transparent cover 72 may then be attached to adhesive layer 78. As shown in Figure 11, cover 72 (which is shown as transparent) may be large enough to cover multiple test strip structures 122. Attaching cover 72 may complete the formation of the plurality of test strip structures 122. The plurality of test strip structures 122 may then be separated from each other to form a plurality of test strips 10, as described above.

3. The meter and removable data storage device

To measure the glucose level in a blood sample, a test strip (e.g., test strip 10, test strip 100, or test strip 110) is preferably used with a meter 200, as shown in Figures 12 and 13. Preferably, meter 200 has a size and shape to allow it to be conveniently held in a user's hand while the user is performing the glucose measurement. Meter 200 may include a front side 202, a back side 204, a left side 206, a right side 208, a top side 210, and a bottom side 212. Front side 202 may include a display 214, such as a liquid crystal display (LCD). Bottom side 212 may include a strip connector 216 into which the test strip is inserted to conduct a measurement.

Left side 206 of meter 200 may include a data connector 218 into which a removable data storage device 220 may be inserted, as described in more detail below. Top side 210 may include one or more user controls 222, such as buttons, with which the user may control meter 200. Right side 208 may include a serial connector (not shown).

5 Figure 14 shows a preferred embodiment of strip connector 216 in more detail. Strip connector 216 includes a channel 230 with a flared opening 231 for receiving a test strip. Tabs 232 and 234 hang over the left and right sides, respectively, of channel 230 at a predetermined height. This predetermined height is set to allow distal end 14 (in thin section 94), but not proximal end 12 (in thick section 96), to be inserted into strip connector 216. In this way, the user may be prevented from improperly inserting the test strip into strip connector 216.

10 Electrical contacts 236 and 238 are disposed in channel 230 behind tabs 232 and 234, and electrical contacts 240 – 246 are disposed in channel 230 behind electrical contacts 236 and 238. When distal end 14 of the test strip is properly inserted into strip connector 216, electrical contacts 236 – 246 contact electrical contacts 32 – 38 and auto-on conductor 48 to electrically connect the test strip to meter 200. In particular, electrical contacts 236 and 238 contact electrical contacts 32 and 34, respectively, to electrically connect working electrode 22 and counter electrode 24 to meter 200. Electrical contacts 240 and 242 contact electrical contacts 36 and 38, respectively, to electrically fill-detect electrodes 28 and 30 to meter 200. Finally, electrical contacts 244 and 246 electrically connect auto-on conductor 48 to meter 200.

15 20 25 Meter 200 may use data from removable data storage device 220 to calculate glucose levels in blood samples measured by meter 200. Specifically, data storage device 220 may be associated with a lot of test strips and may store one or more parameters that meter 200 may use for that lot. For example, data storage device 220 may store one or

more calibration parameters that meter 200 may use to calculate the glucose level from an averaged current measurement. The calibration parameters may include temperature corrections. Data storage device 220 may also store other information related to the lot of test strips and the meter, such as a code identifying the brand of test strips, a code identifying the model of meter to be used, and an expiration date for the lot of test strips.

5 Data storage device 220 may also store other information used by meter 200, such as the duration of the fill timer and the incubation timer, the voltages to use for the "Drop Level 1," "Fill," and "Assay Excitation Level 2" voltages, one or more parameters relating to the number of current measurements to make, and one or more parameters specifying how the meter should average the current measurements, as described in more detail below. Data storage device 220 may also store one or more checksums of the stored data 10 or portions of the stored data.

In a preferred approach, before a given lot of test strips is used with meter 200, the removable data storage device 220 associated with that given lot is first inserted into data connector 218. Meter 200 may then load the relevant data from data storage device 220 into an internal memory when a test strip is inserted into strip connector 216. With the relevant data stored in its internal memory, meter 200 no longer needs data storage device 220 to measure glucose levels using test strips in the given lot. Thus, removable data storage device 220 may be removed from meter 200 and may be used to code other meters. If data storage device 220 is retained in meter 200, meter 200 may no longer 20 access it but instead use the data stored in its internal memory.

With reference to Figure 15, removable data storage device 220 may include a memory chip 250 mounted on a circuit board 252, which, in turn, is mounted to a carrier 254. Memory chip 250 stores the data in a predetermined format. Preferably, memory chip 250 includes a non-volatile memory, so as to retain the stored data when un-

powered. For example, memory chip 250 may be an electronically erasable programmable read only memory (EEPROM) chip. Such EEPROM chips can typically be written to many times (e.g., one million write cycles, or more) so that it does not wear out over the life cycle of usage.

5 Memory chip 250 may be electrically connected to a plurality of electrical contacts on circuit board 252. These electrical contacts may include a voltage supply contact 256, a ground contact 258, a data input/output contact 260, and a clock contact 262. In this way, when the appropriate voltage is applied to voltage supply 256, relative to ground contact 258, data may be synchronously read from or written to memory chip 10 250 using data input/output contact 260 and clock contact 262. As described in more detail below, ground contact 258 may be longer than the other electrical contacts 256, 260, and 262, for greater reliability.

15 Carrier 254 may be made out of a material such as plastic and may include a distal end 264 and a proximal end 266. Distal end 264 is intended to be inserted into data connector 218. Proximal end 266 may include a flange 268 to allow a user's fingers to grip removable data storage device 220 for either insertion into or removal from data connector 218. Carrier 254 may include an opening 270 through which electrical contacts 256 – 262 are accessible. Thus, when data storage device 220 is properly inserted into data connector 218, electrical contacts 256 – 262 on circuit board 252 contact corresponding electrical contacts 272 – 278 (shown in Figure 12), respectively, in data connector 218. In this way, meter 200 may become electrical connected to memory chip 20 250 to read the data stored therein.

25 Carrier 254 and data connector 218 may be "keyed" so that removable data storage device 220 may be inserted into connector 218 in only one orientation. For example, carrier 254 may include a wedge-shaped corner 282 and connector 218 may

include a wedge-shaped opening 284 for receiving wedge-shaped corner 282. As a result, data storage device 220 may fit into data connector 218 only when oriented so that wedge-shaped corner 282 is received in wedge-shaped opening 284. Beneficially, this keying may cue the user as to the proper insertion orientation and may prevent damage 5 that could be caused by improper insertion.

Another feature of removable data storage device 220 that may enhance its reliability is the greater length of ground contact 258. Specifically, circuit board 252 is mounted to carrier 254 such that ground contact 258 extends closer to distal end 264 (i.e., the end inserted into data connector 218) than the other electrical contacts 256, 260, and 10 262. As a result, ground contact 258 is the first electrical contact on circuit board 252 to make electrical contact with meter 200 when data storage device 220 is inserted into data connector 218 and the last electrical contact to break electrical contact with meter 200 when data storage device 220 is removed. This prevents memory chip 250 from being 15 powered in an unintended operating mode that may not be reliable, e.g., the supply voltage from meter 200 being applied to memory chip 250 through voltage supply contact 256 without memory chip 250 also being connected to ground through ground contact 258.

20 **4. The use of the test strip with the meter**

In order to save power, meter 200 is preferably in a low power “sleep” mode most of the time. However, meter 200 may “wake up” and enter an active mode when certain situations occur. For example, actuating one or more of the user controls 222 may cause meter 200 to wake up, as may attempting to use serial port 416 for data transfer. 25 Preferably, inserting either a test strip (e.g., test strip 10, test strip 100, or test strip 110) or

a check strip into meter 200 also wakes it up. Meter 200 may then determine whether the inserted strip is a test strip or a check strip. The flow chart of Figure 16 illustrates this process.

At first, meter 200 is in a low power sleep mode, as indicated by step 300. Then,
5 either a test strip or check strip is inserted into meter 200, as indicated by step 302. The insertion causes the auto-on conductor on the strip (e.g., auto-on conductor 48 on test strip 10) to bridge auto-on contacts 244 and 246 in meter 200. As a result, an auto-on current starts to flow through auto-on contacts 244 and 246 and through the auto-on conductor. This auto-on current causes meter 200 to wake up and enter an active mode,
10 as indicated by step 304.

In this active mode, meter 200 measures the voltage drop across the auto-on conductor, as indicated by step 306. In a preferred approach, the resistance of the auto-on conductors in test strips is significantly different than in check strips. Thus, meter 200 may determine whether the strip inserted into it is a test strip or a check strip based on the
15 auto-on voltage drop. For example, the auto-on conductors in test strips may have a substantially lower resistance than in check strips. Accordingly, meter 200 may compare the auto-on voltage drop to a predetermined threshold value, as indicated by step 308. If the auto-on voltage drop is less than the predetermined threshold value, then meter 200 identifies the strip as a test strip and performs a test strip sequence, as indicated by step
20 310. On the other hand, if the auto-on voltage drop is greater than the predetermined threshold value, then meter 200 identifies the strip as a check strip and performs a check strip sequence, as indicated by step 312.

The flowchart of Figure 17 illustrates a preferred check strip sequence. A check strip may have electrical contacts near its distal end (in addition to the auto-on conductor)
25 that are similar to electrical contacts 32 – 38 on the test strip, except that the electrical

contacts on the check strip may be connected to resistors, with predetermined resistances, rather than to actual electrodes. Thus, when a check strip is inserted into meter 200, electrical contacts 236 and 238 may contact "working electrode" and "counter electrode" contacts on the check strip that are actually connected via a first resistor in the check strip. Similarly, electrical contacts 240 and 242 may contact "fill-detect" contacts on the check strip that are actually connected via a second resistor in the check strip.

As summarized in Figure 17, meter 200 may perform the check strip sequence by measuring the currents through the first and second resistors in the check strip to determine if the measured values fall within acceptable ranges. If the measured current values do not fall within the acceptable ranges, then there may be a problem with meter 200. Thus, meter 200 may first measure the current through working and counter electrode contacts 236 and 238 to obtain a measured current value through the first resistor, as indicated by step 314. Meter 200 then determines if this measured current value is within the acceptable range, as indicated by step 316. If the measured current value is not within the acceptable range, then meter 200 indicates a failure status, as indicated by step 318. To indicate the failure status, meter 200 may display a message or an icon on display 214 and/or provide some other user-discernible failure indication.

If the measured current through the first resistor is within the acceptable range, then meter 200 may also measure the current through fill-detect electrode contacts 240 and 242 to obtain a measured current value through the second resistor, as indicated by step 320. Then, meter 200 determines whether this measured current value is within an acceptable range, as indicated by step 322. If the measured current value is not within the acceptable range, then meter 200 indicates a failure status, as indicated by step 324. If the measured current value is within the acceptable range, then meter 200 may indicate an operational status. For example, meter 200 may display an "OK" icon on display 214.

As noted above, if the meter 200 detects a test strip, then meter 200 performs a test strip sequence. As a first phase of the test strip sequence, meter 200 may validate the working, counter, and fill-detect electrodes by determining whether the impedances between them are sufficiently high. This process is illustrated in the flow chart of Figure 5 18.

As indicated by step 328, meter 200 may apply a predetermined first validation voltage, e.g., the "Drop Level 1" voltage, between working and counter electrodes 22 and 24 and measure any resulting current flowing through working electrode 22. The first validation voltage should result in little or no current, because there should not be a low-10 impedance pathway between working electrode 22 and counter electrode 24. Thus, meter 10 may check whether the resulting current is below a maximum allowable value, as indicated by step 330. If the resulting current is above the maximum value, then meter may indicate a failure status, as indicated by step 332.

Otherwise, meter 200 may proceed with the test strip sequence and apply a predetermined second validation voltage, e.g., the "Fill" voltage, across fill-detect electrodes 28 and 30 and measure any resulting current flowing through fill-detect anode 28, as indicated by step 334. Meter 200 may store this current measurement so that it can be used in subsequent measurements, as described in more detail below. The second validation voltage should result in little or no current, because there should not be any low-impedance pathways between any of the electrodes. However, electronic components, such as amplifiers, in meter 200 may produce small offset currents that are measured in step 334. Meter 200 may check whether the current measurement of step 20 334 is below a maximum allowable value, as indicated by step 336. If the current measurement is above the maximum value, then meter 200 may indicate a failure status, 25 as indicated by step 338. Otherwise, meter 200 may indicate that a blood sample may be

applied to the test strip. For example, meter 200 may display a message or an icon on display 214 and/or provide some other user-discriminable indication.

Meter 200 may perform the measurement of step 334 at the same time it performs the measurement of step 328. Thus, meter 200 may apply the "Drop Level 1" voltage between working and counter electrodes 22 and 24, measuring any resulting current through working electrode 22, while at the same time applying the "Fill" voltage between fill-detect electrodes 28 and 30 and measuring any resulting current through fill-detect anode 28.

If the electrodes are validated, meter 200 may then proceed with the process illustrated in the flow chart of Figure 19. To detect when the user applies the blood sample, meter 200 applies "Drop Level 1" voltage across working electrode 22 and counter electrode 24 and measures any resulting current flowing between these electrodes, as indicated by step 342. Preferably, the "Drop Level 1" voltage is less than the redox potential of the chemistry used in reagent layer 90. At step 344, the user applies a blood sample to the test strip. More particularly, the user may apply the blood sample to the opening of sample chamber 88 at proximal end 12, as shown in Figure 3. As noted above, sample chamber 88 is dimensioned to draw the blood sample into it by capillary action. As the blood sample moves into sample chamber 88, it will eventually bridge working electrode 22 and counter electrode 24, thereby providing an electrically conductive pathway between them. Thus, meter 200 determines that a blood sample is present in sample chamber 88 when the resulting current reaches a predetermined threshold value or series of threshold values with an overall positive magnitude change, as indicated by step 346. When meter 200 detects the blood sample in this way, meter 200 disconnects working and counter electrodes 22 and 24, putting them in a high impedance state relative to fill-detect electrodes 28 and 30, and meter 200 starts a fill

timer and an incubation timer, as indicated by step 348. Before meter 200 puts working and counter electrodes 22 and 24 in the high impedance state, meter 200 may first ground them to discharge stored charges.

The fill timer sets a time limit for the blood sample to traverse reagent layer 90 and reach fill-detect electrodes 28 and 30. The incubation timer sets a delay period to allow the blood sample to react with reagent layer 90. Once meter 200 starts the fill timer running, meter 200 applies a voltage, the "Fill" voltage, between fill-detect electrodes 28 and 30 and measures the resulting current flowing between these electrodes, as indicated by step 350. Meter 200 may subtract from this measured current the current measurement from step 334 to obtain an adjusted current. As indicated by step 352, meter 200 checks whether the current (or adjusted current) reaches a predetermined threshold value or a series of thresholds with an overall positive magnitude change before the fill timer elapses. Preferably, the current threshold(s) are set so that meter 200 can determine whether sufficient sample has reached fill-detect electrodes 28 and 30 and whether the sample has become mixed with the chemical constituents in reagent layer 90.

If the current (or adjusted current) does not reach the required value, then there may be some problem with the test strip. For example, there may be a blockage in sample chamber 88. There may be an inadequate amount of sample. There may be no reagent layer, or the chemical constituents reagent layer may have failed to mix with the blood sample. Any of these problems may make the glucose measurement unreliable. Accordingly, if the fill timer elapses without a sufficient current (or adjusted current) through fill-detect electrodes 28 and 30, meter 200 may indicate a failure status, as indicated by step 354. Meter 200 may indicate this failure status by displaying an error message or icon on display 214 and/or by providing some other user-discernible

indication. The duration of the fill timer may, for example, be in the range of 2 to 6 seconds.

If however, meter 200 detects sufficient current (or adjusted current) through fill-detect electrodes 28 and 30 before the fill timer elapses, then meter 200 may proceed with the glucose measurement process. As indicated by step 356, meter 200 may provide an indication to the user that meter 200 has detected adequate sample mixed with the chemical constituents of reagent layer 90. For example, meter 200 may beep, display a message or icon on display 214, or provide some other user-discernible indication. Preferably, meter 200 also disconnects fill-detect electrodes 28 and 30, bringing them to a high impedance state relative to working electrode 22 and counter electrode 24. Meter 200 may ground fill-detect electrodes 28 and 30 before putting them into the high impedance state in order to discharge stored charges. Meter 200 then waits for the incubation timer to elapse, as indicated by step 358, in order to allow sufficient time for the blood sample to react with reagent layer 90. The incubation timer may, for example, take about 2 seconds to about 10 seconds to elapse, depending on the implementation. In a preferred embodiment, the incubation timer lasts about 5 seconds.

When the incubation timer elapses, meter 200 applies the "Assay Excitation Level 2" voltage between working electrode 22 and counter electrode 24 and measures the resulting current flowing between these electrodes, as indicated by step 360. Preferably, meter 200 measures the resulting current at a fixed sampling rate throughout a measurement period, to obtain a plurality of current measurements. The measurement period may last from about 5 seconds to about 15 seconds, depending on the implementation. In a preferred embodiment, the measurement period lasts about 5 seconds.

Meter 200 then determines the glucose level in the blood sample from the current measurements, as indicated by step 362. In a preferred approach, meter 200 may average the current measurements to obtain an average current value at a predetermined point of time during the measurement period. Meter 200 may then use the calibration data obtained from removable data storage device 220 and stored in its internal memory to calculate the glucose level from the average current value. Meter 200 may also take a temperature reading and use the temperature reading to correct the measured glucose level for temperature dependence. In addition, meter 200 may check the validity of the current measurements by checking that the measured current decreases over time, as expected.

For example, in a preferred embodiment, meter 200 may take a predetermined number of current measurements ($m_1 \dots m_M$) in 0.1 second time intervals. The predetermined number, M , may, for example, range from 50 to 150, and it may be a parameter specified in removable data storage device 220. The meter may then average every n current measurements to provide a plurality of data points ($d_1 \dots d_N$). Thus, if n is equal to 3, the meter would calculate d_1 by averaging m_1 , m_2 , and m_3 , and would calculate d_2 by averaging m_2 , m_3 , and m_4 . The averaging parameter, n , may be a parameter specified in removable data storage device 220. One of the data points may then be selected as the center point for another level of averaging, in which the meter averages together the data points around and including the center point to provide a meter reading, X . Thus, if d_2 is selected as the center point, then the meter may average d_1 , d_2 , and d_3 together to calculate the meter reading, X . Removable data storage device 220 may store a parameter that specifies which of the data points to use as the center point for calculating the meter reading, X . Meter 200 then calculates the glucose level, Y , from the meter reading, X , and one or more calibration parameters, which may be specified in

removable data storage device 220. For example, in an exemplary embodiment, meter 200 may use three calibration parameters, a , b , and c , to calculate Y , using the expression $a + bX + cX^2$. Alternatively, different expressions, which may include different terms and/or different numbers of calibration parameters, may be used to calculate Y . For 5 example, in another exemplary embodiment, Y may be calculated using the expression $a + bX + cX^2 + d/X$. In some cases, data storage device 220 may specify what expression to use to calculate Y in addition to what calibration parameters to use.

The glucose level, Y , calculated in this way may not be temperature corrected, however. To correct for temperature, meter 200 may apply one or more temperature 10 correction parameters, which may be specified in removable data storage device 220. For example, in a preferred embodiment, the temperature-corrected glucose level may be calculated from the expression $A + BT + CYT + DY$, where A , B , C , and D are temperature correction parameters and T is a measured temperature. The calibration parameters A , B , C , and D may be specified in removable data storage device 220. In other embodiments, 15 the temperature correction may use only a single parameter, S , which may be specified in removable data storage device 220. For example, the temperature-corrected glucose level may be calculated from the expression $Y/[(1 + S(T - 21))]$.

If the current measurements appear valid, then meter 200 displays the glucose 20 level, typically as a number, on display 214, as indicated by step 364. Meter 200 may also store the measured glucose level, with a timestamp, in its internal memory.

5. Meter electronics

Figure 20 shows, in simplified form, the electronic components of meter 200, in accordance with a preferred embodiment. Meter 200 may include a microcontroller 400 that controls the operation of meter 200 in accordance with programming, which may be 25 provided as software and/or firmware. Microcontroller 400 may include a processor 402,

a memory 404, which may include read-only memory (ROM) and/or random access memory (RAM), a display controller 406, and one or more input/output (I/O) ports 408. Memory 404 may store a plurality of machine language instructions that comprises the programming for controlling the operation of meter 200. Memory 404 may also store data. Processor 402 executes the machine language instructions, which may be stored in memory 404 or in other components, to control microcontroller 400 and, thus, meter 200. In particular, processor 402 may execute the stored machine language instructions so that meter 200 performs the functions summarized in the flowcharts of Figures 16-19 and described above.

Microcontroller 400 may also include other components under the control of processor 402. For example, microcontroller 400 may include a display controller 406 to help processor 402 control display 214. In a preferred embodiment, display 214 is an LCD and display controller 406 is an LCD driver/controller. Microcontroller may also include I/O ports 408, which enable processor 402 to communicate with components external to microcontroller 400. Microcontroller 400 may also include one or more timers 410. Processor 402 may use timers 410 to measure the fill time period, incubation time period, and other time periods described above. Microcontroller 400 may be provided as an integrated circuit, such as the HD64F38024H, available from Hitachi.

Microcontroller 400 is preferably connected to components that provide a user interface. The components that make up the user interface of meter 200 may include display 214, a beeper 412, and user controls 222. Microcontroller 400 may display text and/or graphics on display 214. Microcontroller may cause beeper 412 to beep, such as to indicate that adequate sample (mixed with the chemistry of reagent layer 90) has reached fill-detect electrodes 28 and 30, as described above. Microcontroller 400 may also be connected to other components, such as one or more light-emitting diodes

(LEDs), to provide user-discriminable indications, which may be visible, audible, or tactile. Microcontroller 400 may receive user input from user controls 222. In a preferred embodiment, user controls 222 consists of a plurality of discrete switches. However, user controls 222 may also include a touch screen or other components with which a user can 5 provide input to meter 200.

Microcontroller 400 may have access to one or more memories external to it, such as an EEPROM 414. In a preferred embodiment, microcontroller 400 stores the measured glucose levels, and the times and dates the glucose measurements occurred, in EEPROM 414. By using user controls 222, the user may also be able to cause 10 microcontroller 400 to display one or more of the glucose measurements stored in EEPROM 414 on display 214. Microcontroller 400 may also be connected to a serial port 416, through which the user can access the glucose measurements stored in EEPROM 414. Microcontroller 400 may use a transmit line, "TX," to transmit signals to serial port 416 and may use a receive line, "RX," to receive signals from serial port 416.

EEPROM 414 may also store the data from removable data storage device 220. In this regard, Figure 20 shows how electrical contacts 272 – 278 of data connector 216 are connected inside of meter 200. Contact 272 is connected to a source of power, which may be through microcontroller 400. In this way, microcontroller 400 can do "power management," powering removable data storage device 220, through contact 272, only 20 when necessary, e.g., when downloading data from removable data storage device 220. Contact 274 is connected to ground. Contacts 276 and 278 are connected to data input/output and clock outputs, respectively, of microcontroller 400. In this way, microcontroller 400 may download the data from data storage device 220, when connected to data connector 216, and store the data in EEPROM 414.

In a preferred embodiment, meter 200 also includes a data acquisition system (DAS) 420 that is digitally interfaced with microcontroller 400. DAS 420 may be provided as an integrated circuit, such as the MAX1414, available from Maxim Integrated Products, Sunnyvale, California.

5 DAS 420 includes one or more digital-to-analog converters (DACs) that generate analog voltages in response to digital data from microcontroller 400. In particular, DAS 420 includes "Vout1" and "FB1" terminals, which DAS 420 uses to apply analog voltages generated by a first DAC to working electrode 22, when the test strip is inserted in strip connector 216. Similarly, DAS 420 includes "Vout2" and "FB2" terminals,
10 which DAS 420 uses to apply analog voltages generated by a second DAC to fill-detect anode 28, when a test strip is inserted in strip connector 216. The one or more DACs in DAS 420 generate analog voltages based on digital signals provided by microcontroller 400. In this way, the voltages generated by the one or more DACs may be selected by processor 402.

15 DAS 420 also includes one or more analog-to-digital converters (ADCs) with which DAS 420 is able to measure analog signals. As described in more detail below, DAS 420 may use one or more ADCs connected to the "Vout1" and "Vout2" terminals to measure currents from working electrode 22 and counter electrode 24, respectively, when a test strip is inserted in strip connector 216. DAS 420 may also include one or more
20 other terminals through which the ADCs may measure analog signals, such as the "Analog In1" and "Analog In2" terminals shown in Figure 20. DAS 420 may use the "Analog In1" terminal to measure the voltage across the auto-on conductor in a test strip or check strip that is connected to strip connector 216. The "Analog In2" terminal may be connected to a thermistor, RT1, to enable DAS 420 to measure temperature. In
25 particular, DAS 420 may supply a reference voltage, V_{ref} , through a voltage divider that

includes thermistor, RT1, and another resister, R_d. DAS 420 may use the “Analog In2” terminal to measure the voltage across thermistor, RT1. DAS 420 transfers the digital values obtained from the one or more ADCs to microcontroller 400, via the digital interface between these components.

5 Preferably, DAS 420 has at least two modes of operation, a “sleep” or low-power mode and an “active” or run mode. In the active mode, DAS 420 has full functionality. In the sleep mode, DAS 420 has reduced functionality but draws much less current. For example, while DAS 420 may draw 1 mA or more in the active mode, DAS 420 may draw only microamps in the sleep mode. As shown in Figure 20, DAS 420 may include 10 “Wake-up1,” “Wake-up2,” and “Wake-up3” inputs. When appropriate signals are asserted at any of these “Wake-up” terminals, DAS 420 may wake up from the sleep mode, enter the active mode, and wake up the rest of meter 200, as described in more detail below. In a preferred embodiment, the “Wake-up” inputs are active-low inputs that are internally pulled up to the supply voltage, V_{CC}. As described in more detail below, 15 inserting the auto-on conductor in either a test strip or check strip into strip connector 216 causes the “Wake-up1” input to go low and, thereby, causing DAS 420 to enter the active mode. In addition, the “Wake-up2” input may be connected to one or more of user controls 222. In this way, the user’s actuation of at least certain of user controls 222 causes DAS 420 to enter the active mode. Finally, the “Wake-up3” input may be 20 connected to serial port 416, e.g., via receive line, “RX.” In this way, attempting to use serial port 416 for data transfer may wake up DAS 420 and, hence, meter 200.

25 As shown in Figure 20, DAS 420 includes several terminals that are connected to microcontroller 400. DAS 420 includes one or more ‘Data I/O’ terminals, through which microcontroller 400 may write digital data to and read digital data from DAS 420. DAS 420 also includes a “Clock In” terminal that receives a clock signal from microcontroller

400 to coordinate data transfer to and from the “Data I/O” terminals. DAS 420 may also include a “Clock Out” terminal through which DAS 420 may supply a clock signal that drives microcontroller 400. DAS 420 may generate this clock signal by using a crystal 422. DAS 420 may also generate a real time clock (RTC) using crystal 422.

5 DAS 420 may also include other terminals through which DAS 420 may output other types of digital signals to microcontroller 400. For example, example DAS 420 may include a “Reset” terminal, through which DAS 420 may output a signal for resetting microcontroller 400. DAS 420 may also include one or more “Interrupt Out” terminals, which DAS 420 may use to provide interrupt signals to microcontroller 400. DAS 420
10 may also include one or more “Data Ready” inputs that DAS 420 may use to signal microcontroller 400 that DAS 420 has acquired data, such as from an analog-to-digital conversion, which is ready to be transferred to microcontroller 400.

As shown in Figure 20, meter 200 may include a power source, such as one or more batteries 424. A voltage regulator 426 may provide a regulated supply voltage,
15 V_{CC} , from the voltage supplied by batteries 424. The supply voltage, V_{CC} , may then power the other components of meter 200. In a preferred embodiment, voltage regulator 426 is a step-up DC-to-DC voltage converter. Voltage regulator 426 may be provided as an integrated circuit and other components, such as an inductor, capacitors, and resistors. The integrated circuit may, for example, be a MAX1724, available from Maxim
20 Integrated Products, Sunnyvale, California.

Preferably, voltage regulator 426 has a shutdown mode, in which it provides only an unregulated output voltage. DAS 420 may include a “Shutdown” terminal through which DAS 420 may control voltage regulator 426. In particular, when DAS 420 enters the sleep mode, DAS 420 may assert a low level signal at its “Shutdown” terminal, causing voltage regulator 426 to enter the shutdown mode. When DAS 420 enters the
25

active mode, it asserts a high level signal at its “Shutdown” terminal, allowing voltage regulator 426 to operate normally.

Figure 20 also shows how electrical contacts 236 – 246 of strip connector 216 are connected in meter 200. Contacts 236 and 238, which are electrically connected to working electrode 22 and counter electrode 24, respectively, when the test strip is inserted in strip connector 216, are connected as follows. Contact 236, for working electrode 22, is connected to the “FB1” terminal of DAS 420 and connected via a resistor, RF1, to the “Vout1” terminal of DAS 420. Contact 238, for counter electrode 24, is connected to a switch 428. Switch 428 allows contact 238 (and, hence, counter electrode 24) to be connected to ground or left in a high impedance state. Switch 428 may be digitally controlled by microcontroller 400, as shown in Figure 20. With counter electrode 24 connected to ground, DAS 420 may use the “Vout1” and “FB1” terminals to apply voltages to working electrode 22 (relative to counter electrode 24) and to measure the current through working electrode 22.

Contacts 240 and 242, which are electrically connected to fill-detect anode 28 and fill-detect cathode 30, respectively, when the test strip is inserted in strip connector 216, are connected as follows. Contact 240, for fill-detect anode 28, is connected to the “FB2” terminal of DAS 420 and connected via a resistor, RF2, to the “Vout2” terminal of DAS 420. Contact 242, for fill-detect cathode 30, is connected to a switch 430. Switch 430 allows contact 242 (and, hence, fill-detect cathode 30) to be connected to ground or left in a high impedance state. Switch 430 may be digitally controlled by microcontroller 400, as shown in Figure 20. With fill-detect cathode 30 connected to ground, DAS 420 may use the “Vout2” and “FB2” terminals to apply voltages to fill-detect anode 28 (relative to fill-detect cathode 30) and to measure the current through fill-detect anode 28.

Switches 428 and 430 may be single-pole/single-throw (SPST) switches, and they may be provided as an integrated circuit, such as the MAX4641, available from Maxim Integrated Products, Sunnyvale, California. However, other configurations for switches 428 and 430 could be used.

5 Contacts 244 and 246, which are electrically connected to the auto-on conductor when a test strip or check strip is inserted into strip connector 216, are connected as follows. Contact 246 is connected to ground or other reference potential. Contact 244 is connected to the "Analog In1" and "Wake-up1" terminals of DAS 420 and to microcontroller 400. As described in more detail below, the presence of the auto-on 10 conductor drives the "Wake-up1" terminal low, thereby waking up DAS 420 and causing it to enter an active mode. DAS 420 uses the "Analog In1" terminal to measure the voltage across the auto-on conductor. By virtue of its connection to contact 244, microcontroller 400 is able to determine whether the auto-on conductor is present, and, thus, whether either a test strip or check strip is connected to strip connector 216.

15 Figure 21 shows in greater detail the functional aspects of the connections between meter 200 and electrodes 22, 24, 28, and 30, when the test strip is inserted in strip connector 216. As shown in Figure 21, DAS 420 functionally includes an amplifier 440 for working electrode 22 and an amplifier 442 for fill-detect anode 28. More particularly, the output of amplifier 440 is connected to working electrode 22, via the "Vout1" terminal and resistor, RF1, and the inverting input of amplifier 440 is connected to working electrode 22, via the "FB1" terminal. Similarly, the output of amplifier 442 is connected to fill-detect anode 28, via the "Vout2" terminal and resistor, RF2, and the inverting input of amplifier 442 is connected to fill-detect anode 28, via the "FB2" 20 terminal.

To generate selected analog voltages to apply to working electrode 22 and fill-detect electrode 28, DAS 420 includes a first DAC 444 and a second DAC 446, respectively. DAC 444 is connected to the non-inverting input of amplifier 440, and DAC 446 is connected to the non-inverting input of amplifier 442. In this way, amplifier 440 applies a voltage to the "Vout1" terminal, such that the voltage at working electrode 22, as sensed at the inverting input of amplifier 440, is essentially equal to the voltage generated by DAC 444. Similarly, amplifier 442 applies a voltage to the "Vout2" terminal, such that the voltage at fill-detect electrode 28, as sensed at the inverting input of amplifier 442, is essentially equal to the voltage generated by DAC 446.

To measure the currents through working electrode 22 and fill-detect anode 28, DAS 420 includes an ADC 448 and multiplexers (MUXes) 450 and 452. MUXes 450 and 452 are able to select the inputs of ADC 448 from among the "Vout1," "FB1," "Vout2," and "FB2" terminals. DAS 420 may also include one or more buffers and/or amplifiers (not shown) between ADC 448 and MUXes 450 and 452. To measure the current through working electrode 22, MUXes 450 and 452 connect ADC 448 to the "Vout1" and "FB1" terminals to measure the voltage across resistor, RF1, which is proportional to the current through working electrode 22. To measure the current through fill-detect electrode 28, MUXes 450 and 452 connect ADC 448 to the "Vout2" and "FB2" terminals to measure the voltage across resistor, RF2, which is proportional to the current through fill-detect anode 28.

As noted above, meter 200 preferably includes switches 428 and 430 that may be used to bring counter electrode 24 and fill-detect cathode 30, respectively, into a high impedance state. It is also preferable for meter 200 to be able to bring working electrode 22 and fill-detect anode 28 into a high impedance state as well. In a preferred embodiment, this may be achieved by DAS 420 being able to bring terminals "Vout1,"

“FB1,” “Vout2,” and “FB2” into high impedance states. Accordingly, DAS 420 may effectively include switches 454, 456, 458, and 460, as shown in Figure 21. Although switches 428, 430, and 454 – 460 may be SPST switches, as shown in Figure 21, other types of switches, such as single pole-double throw (SPDT) switches, may be used, and the switches may be arranged in other ways, in order to provide meter 200 with the ability to select one pair of electrodes (either the working and counter electrode pair or the fill-detect electrode pair) and leave the other pair of electrodes in a high impedance state. For example, a pair of SPDT switches may be used, with one SPDT switch selecting which of working electrode 22 and fill-detect 28 to connect to DAS 420 and the other SPDT switch selecting which of counter electrode 24 and fill-detect cathode to connect to ground. In other cases, meter 200 may not be configured to bring all of the electrodes into high impedance states. For example, in some embodiments, meter 200 may not include switch 428, with the result that counter electrode 24 is always connected to ground when the test strip is inserted in strip connector 216.

Figure 22 shows in greater detail the functional aspects of the connections between meter 200 and the auto-on conductor when either a test strip or a check strip is inserted in strip connector 216. As shown in Figure 22, the auto-on conductor provides an effective resistance, R_{auto} , between contacts 244 and 246 of strip connector 216. Within meter 200, contact 244 is connected to the source voltage, V_{cc} , through an effective resistance, R_S . For example, the “Wake-up1” terminal of DAS 420, to which contact 244 is connected, may be internally pulled up to V_{cc} , through an effective resistance, R_S . Accordingly, when either a test strip or a check strip is inserted into strip connector 216, such that the auto-on conductor bridges contacts 244 and 246, a current flows through the auto-on resistor and a voltage drop develops between contacts 244 and 246. The magnitude of this auto-on voltage drop depends on the relative magnitudes of

R_{auto} and R_S. Preferably, R_{auto} is chosen sufficiently low for the test strips and check strips, relative to R_S, such that the auto-on voltage is less than the logic low voltage (which may be about 0.8 volts) used in meter 200. It is also preferable for R_{auto} to be substantially different in test strips and check strips, so that meter 200 may determine the strip type from the auto-on voltage drop. For example, if R_S is about 500 kΩ, then R_{auto} 5 may be less than about 20 Ω in a test strip and may be approximately 20 kΩ in a check strip. In this way, microcontroller 400 may determine that either a test strip or check strip is inserted in strip connector 216 by sensing a logic low voltage at contact 244.

DAS 420 also senses the auto-on voltage drop and uses it to wake up meter 200 10 and to determine the strip type, i.e., whether a test strip or a check strip has been inserted into strip connector 216. In the case of a test strip, DAS 420 may also confirm that the test strip has been properly inserted into strip connector 216.

DAS 420 may include wake-up logic 462, which senses the voltage at the "Wake-up1" terminal, via one or more buffers and/or amplifiers, such as buffer 464. DAS 420 15 also includes ADC 448, which can measure the voltage at the "Analog In1" terminal, via one or more buffers and/or amplifiers, such as buffer 466. Although not shown in Figure 22, MUXes 450 and 452 may be connected between buffer 466 and ADC 448.

When no strip is present in strip connector 216, contact 244 (and, thus, the "Wake-up1" terminal) is at a high voltage, at or near V_{CC}. However, when either a test 20 strip or a check strip is inserted in strip connector 216, the auto-on conductor drives the voltage at the "Wake-up1" terminal low, as described above. Wake-up logic 462 senses the voltage at the "Wake-up1" terminal going low and, in response, initiates a wake-up sequence to bring DAS 420 into an active mode. As part of this wake-up sequence, wake-up logic 462 may cause DAS 420 to assert a signal at its "Shutdown" terminal to 25 turn on voltage regulator 426. Wake-up logic 462 may also cause DAS 420 to generate

signals to wake up microcontroller 400. For example, wake-up logic 462 may cause DAS 420 to assert a clock signal through its "Clock Out" terminal, a reset signal through its "Reset" terminal, and an interrupt signal through its "Interrupt Out" terminal to activate microcontroller 400.

5 Though not shown in Figure 22, wake-up logic 462 may also sense the voltages at the "Wake-up1" and "Wake-up2" terminals and, in response to a voltage at one of these terminals going low, may initiate a wake-up sequence similar to that described above.

When DAS 420 enters the active mode, it also determines the type of strip inserted into strip connector 216. In particular, ADC 448 measures the voltage at the 10 "Analog In1" terminal. DAS 420 then reports the measured voltage to microcontroller 400. Based on this information, microcontroller 400 then initiates either a test strip sequence or a check strip sequence, as described above. Throughout either sequence, microcontroller 400 may periodically check the voltage at contact 244 to make sure that the strip is still inserted in strip connector 216. Alternatively, an interrupt may notify 15 microcontroller 400 of a voltage increase at contact 244 caused by removal of the strip.

In this way, the auto-on voltage drop developed across the auto-on conductor performs several functions in meter 200. First, the auto-on voltage wakes up meter 200 from a sleep mode to an active mode. Second, meter 200 determines the strip type from the magnitude of the auto-on voltage. Third, the auto-on voltage lets meter 200 know that 20 the strip is still inserted in strip connector 216, as meter 200 proceeds with either the test strip or check strip sequence.

6. Conclusion

Preferred embodiments of the present invention have been described above. Those skilled in the art will understand, however, that changes and modifications may be made to

these embodiments without departing from the true scope and spirit of the invention, which is defined by the claims.

CLAIMS

1. A test strip for measuring glucose in a blood sample, said test strip comprising:

a first insulating sheet, said first insulating sheet having a proximal end and a distal end, said proximal end being narrower than said distal end;

5 at least four electrodes disposed on said first insulating sheet, said at least four electrodes including a working electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode;

10 a plurality of electrical contacts disposed on said first insulating sheet, said plurality of electrical contacts including a working electrode contact, a counter electrode contact, a fill-detect anode contact, and a fill-detect cathode contact;

15 a plurality of conductive traces disposed on said first insulating sheet, said plurality of conductive traces electrically connecting said working electrode to said working electrode contact, said counter electrode to said counter electrode contact, said fill-detect anode to said fill-detect anode contact, said fill-detect cathode to said fill-detect cathode contact;

an auto-on conductor disposed on said first insulating sheet;

20 a first dielectric layer disposed on said first insulating sheet, said first dielectric layer covering portions of said working electrode and said counter electrode, so as to define an exposed working electrode portion and an exposed counter electrode portion;

25 a second dielectric layer disposed on said first dielectric layer, said second dielectric having a slot, said working electrode, said counter electrode, said fill-detect anode, and said fill-detect cathode being disposed in said slot, said slot having a proximal end and a distal end, said proximal end of said slot being aligned with said proximal end of said first insulating sheet;

a reagent layer disposed in said slot, said reagent layer including glucose oxidase and a mediator; and

5 a second insulating sheet attached to said second dielectric layer, said second insulating sheet covering said slot except for said distal end of said slot,

wherein said slot defines a sample chamber in said test strip and said distal end of said slot vents said sample chamber, said slot being dimensioned to draw said blood sample in through said proximal end of said slot by capillary action.

10 2. The test strip of claim 1, wherein said counter electrode includes a first section and a second section, said working electrode being disposed on said first insulating sheet between said first second and said second section.

15 3. The test strip of claim 1, wherein said at least four electrodes are formed by a first conductive ink printed on said first insulating sheet.

4. The test strip of claim 3, wherein said first conductive ink contains graphite.

20 5. The test strip of claim 4, wherein said electrical contacts, said conductive traces, and said auto-on conductor are formed by a second conductive ink printed on said first insulating sheet.

25 6. The test strip of claim 5, wherein said second conductive ink contains silver.

7. The test strip of claim 1, wherein said test strip has a thick section and a thin section, said thick section including said proximal end, said thin section including said distal end, said electrical contacts and said auto-on conductor being located in said thin section.

5

8. The test strip of claim 1, wherein said reagent layer covers said exposed working electrode portion.

9. The test strip of claim 1, wherein said second insulating sheet is
10 transparent.

10. A test strip for testing a blood sample, said test strip comprising:
a sample chamber for said blood sample;
at least four electrodes for measuring at least one electrical characteristic of said
15 blood sample in said sample chamber, said at least four electrodes including a working
electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode;
a plurality of electrical contacts electrically connected to said at least four
electrodes; and
at least one auto-on electrical contact electrically isolated from said at least four
20 electrodes.

11. The test strip of claim 10, further comprising:
a reagent layer disposed in said sample chamber.

12. The test strip of claim 10, wherein said sample chamber has a first opening for receiving said blood sample and a second opening for venting said sample chamber.

13. The test strip of claim 12, wherein said sample chamber is dimensioned to
5 draw said blood sample in through said first opening by capillary action.

14. The test strip of claim 12, wherein said test strip has a proximal end and a distal end, said first opening being located at said proximal end.

10 15. The test strip of claim 14, wherein said proximal end is narrower than said distal end.

16. The test strip of claim 14, wherein said test strip has a thick section and a thin section, said thin section including said proximal end.

15 17. The test strip of claim 16, wherein said plurality of electrical contacts and said at least one auto-on electrical contact are located in said thin section.

18. A method of making a plurality of test strips, said method comprising:
20 forming a plurality of test strip structures on a first insulating sheet, wherein each test strip structure is formed by:

(a) forming a first conductive pattern on said first insulating sheet, said first conductive pattern including at least four electrodes, said at least four electrodes including a working electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode;

(b) forming a second conductive pattern on said first insulating sheet, said second conductive pattern including a plurality of electrode contacts for said at least four electrodes, a plurality of conductive traces electrically connecting said at least four electrodes to said plurality of electrode contacts, and an auto-on conductor;

5 (c) applying a first dielectric layer over portions of said working electrode and said counter electrode, so as to define an exposed working electrode portion and an exposed counter electrode portion;

10 (d) applying a second dielectric layer to said first dielectric layer, said second dielectric layer defining a slot, said working electrode, said counter electrode, said fill-detect anode, and said fill-detect cathode being disposed in said slot;

(e) forming a reagent layer in said slot, said reagent layer including glucose oxidase and a mediator; and

15 (f) attaching a second insulating sheet to said second dielectric layer, such that said second insulating sheet covers said slot except for a distal end of said slot; and

separating said plurality of test strip structures into said plurality of test strips, each of said test strips having a proximal end and a distal end, with said slot extending to said proximal end, said proximal end being narrower than said distal end.

20 19. The method of claim 18, wherein forming a first conductive pattern on said first insulating sheet comprises:

printing a first conductive ink on said first insulating sheet, said first conductive ink containing graphite.

20. The method of claim 19, wherein forming a second conductive pattern on said second insulating sheet comprises:

printing a second conductive ink on said second insulating sheet, said second conductive ink containing silver.

5

21. A method of making a plurality of test strips, said method comprising: forming a plurality of test strip structures on one sheet, each of said test strip structures including:

- (a) a sample chamber;
 - (b) a plurality of electrodes, including a working electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode;
 - (c) a plurality of electrical contacts electrically connected to said plurality of electrodes; and
 - (d) at least one auto-on electrical contact, electrically isolated from said plurality of electrodes; and
- separating said test strip structures into said plurality of test strips.

22. The method of claim 21, wherein each of said test strip structures includes a reagent layer disposed in said sample chamber.

20

23. The method of claim 21, wherein separating said test strip structures into said plurality of test strips comprises:

punching said plurality of test strip structures to form a plurality of tapered test strip structures, each of said tapered test strip structures having a tapered section.

25

24. The method of claim 23, wherein separating said test strip structures into said plurality of test strips further comprises:

slitting said plurality of tapered test strip structures into said plurality of test strips.

5 25. A method of measuring glucose in a blood sample, said method comprising:

providing a test strip, said test strip having a sample chamber, with a working electrode, a counter electrode, a pair of fill-detect electrodes, and a reagent layer disposed in said sample chamber, said reagent layer including glucose oxidase and a mediator, said 10 test strip including an auto-on conductor;

inserting said test strip into a meter, said meter being in a sleep mode;

said meter detecting an auto-on current through said auto-on conductor and responsively entering an active mode;

15 said meter validating said working and counter electrodes by applying a first validation voltage between said working and counter electrodes;

said meter validating said fill-detect electrodes by applying a second validation voltage between said fill-detect electrodes, while said first validation voltage is applied between said working and counter electrodes;

applying said blood sample to said sample chamber;

20 said meter detecting said blood sample at a first location in said sample chamber by applying a drop-detect voltage between said working and counter electrodes and measuring a drop-detect current flowing between said working and counter electrodes;

25 said meter detecting said blood sample at a second location in said sample chamber by applying a fill-detect voltage between said fill-detect electrodes and measuring a fill-detect current flowing between said fill-detect electrodes;

after waiting an incubation time period, said meter applying an assay voltage between said working and counter electrodes and making at least one measurement of the resulting current through said working electrode; and

said meter determining a measured glucose level from said at least one current
5 measurement.

26. The method of claim 25, further comprising:

said auto-on current developing an auto-on voltage drop across said auto-on conductor; and

10 said meter measuring said auto-on voltage drop.

27. The method of claim 25, further comprising:

said meter measuring any leakage current through said working electrode, while applying said first validation voltage between said working and counter electrodes; and

15 if said leakage current exceeds a first predetermined level, said meter indicating an error condition.

28. The method of claim 25, further comprising:

20 said meter measuring any leakage current through one of said fill-detect electrodes, while applying said first validation voltage between said working and counter electrodes and said second validation voltage between said fill-detect electrodes; and

if said leakage current exceeds a second predetermined level, said meter indicating an error condition.

25 29. The method of claim 25, further comprising:

if said drop-detect current does not reach a drop-detect threshold value within a predetermined time period, said meter indicating an error condition.

30. The method of claim 25, further comprising:

5 if said drop-detect current reaches a drop-detect threshold value within a predetermined time period, said meter:

- a) switching said working and counter electrodes to a high impedance state relative to said fill-detect electrodes;
- b) starting a fill time period; and
- c) 10 starting said incubation time period.

31. The method of claim 30, further comprising:

if said fill-detect current does not reach a fill-detect threshold value within said fill time period, said meter indicating an error condition.

15

32. The method of claim 30, further comprising:

if said fill-detect current reaches a fill-detect threshold value within said fill time period, said meter providing a user-discernible indication.

20

33. A method of using a test strip to test a blood sample, said test strip including a sample chamber, a working electrode, a counter electrode, a pair of fill-detect electrodes, and an auto-on conductor, said method comprising:

inserting said test strip into a meter, said meter being in a sleep mode;

said meter detecting an auto-on current through said auto-on conductor and

25 responsively entering an active mode;

applying said blood sample to said sample chamber;
said meter detecting said blood sample in said sample chamber by applying a fill-detect voltage between said fill-detect electrodes and measuring a fill-detect current flowing between said fill-detect electrodes;

5 said meter applying an assay voltage between said working and counter electrodes and making at least one measurement of the resulting current; and
said meter determining a test result from said at least one current measurement.

34. The method of claim 33, further comprising:

10 said auto-on current developing an auto-on voltage drop across said auto-on conductor; and
said meter measuring said auto-on voltage drop.

35. The method of claim 33, further comprising:

15 if said fill-detect current reaches a fill-detect threshold value within a predetermined time period, said meter providing a user-discriminable indication.

36. The method of claim 33, further comprising:

20 said meter detecting said blood sample in said sample chamber by applying a drop-detect voltage between said working and counter electrodes and measuring a drop-detect current flowing between said working and counter electrodes.

37. The method of claim 36, further comprising:

25 if said drop-detect current reaches a drop-detect threshold value within a predetermined time period, said meter starting an incubation time period.

38. The method of claim 37, wherein said meter applies said assay voltage after said incubation time period.

39. A method of strip identification, said method comprising:

5 inserting a strip into a meter, said strip including an auto-on conductor, said meter being in a sleep mode;

said meter detecting said strip, by detecting a current flow through said auto-on conductor, and responsive entering an active mode;

said meter measuring a voltage drop across said auto-on conductor;

10 said meter identifying said strip as either a test strip or a check strip based on said voltage drop;

if said strip is a test strip, said meter performing a test strip sequence; and

if said strip is a check strip, said meter performing a check strip sequence.

15 40. The method of claim 39, wherein said meter identifies said strip as a test strip if said voltage drop is below a predetermined value.

41. The method of claim 40 wherein said meter identifies said strip as a check strip if said voltage drop is above said predetermined value.

20 42. A removable data storage device for a meter, said meter measuring using test strips to measure glucose levels in blood samples, said removable data storage device comprising:

a carrier having a proximal end and a distal end, said carrier being keyed for
25 inserting said distal end into said meter in a preferred orientation;

a circuit board mounted to said carrier, said circuit board including a plurality of electrical contacts for electrically connecting to said meter, said plurality of electrical contacts including a ground contact and a voltage supply contact, said ground contact extending closer to said distal end than said voltage supply contact; and

5 a memory mounted to said circuit board and electrically connected to said plurality of electrical contacts, said memory storing data for use by said meter, said data including at least one calibration parameter for use with at least one test strip,

whereby when said removable data storage device is inserted into said meter in
said preferred orientation, said ground contact becomes electrically connected to said
10 meter before said voltage supply contact.

43. The removable data storage device of claim 42, wherein said at least one
calibration parameter corrects for temperature.

15 44. The removable data storage device of claim 42, wherein said data
identifies a brand of said at least one test strip.

45. The removable data storage device of claim 42, wherein said data
identifies a model of said meter.

20 46. The removable data storage device of claim 42, wherein said data
identifies an expiration date of said at least one test strip.

47. The removable data storage device of claim 42, wherein said data specifies
25 at least one time period duration to be used by said meter.

48. The removable data storage device of claim 42, wherein said data specifies at least one voltage to be used by said meter.

5 49. The removable data storage device of claim 42, wherein said data specifies a number of current measurements to be taken by said meter.

10 50. The removable data storage device of claim 49, wherein said data specifies an averaging method of said current measurements.

15 51. A meter for use in combination with a test strip for measuring a glucose level in a blood sample applied to a sample chamber in said test strip, said test strip having at least four electrodes disposed in said sample chamber, said at least four electrodes including a working electrode, a counter electrode, and a pair of fill-detect electrodes, said test strip having a thin section and a thick section, said thin section including a plurality of test strip contacts for said at least four electrodes and an auto-on conductor, said meter comprising:

20 a first connector for receiving said test strip, said first connector including meter contacts for electrically connecting to said test strip contacts and said auto-on conductor, said first connector being sized to receive said thin section but not said thick section of said test strip;

25 a second connector for receiving a removable data storage device, said removable data storage device storing data for use by said meter;

a processor;

25 a memory;

a display;
a plurality of machine language instructions stored in said memory and executable by said processor for:

- a) saving said data from said removable data storage device into said memory;
- 5 b) performing a test strip sequence when said test strip is inserted in said first connector to obtain at least one current measurement related to said glucose level;
- c) determining a glucose level in said blood sample from said at least one current measurement and said data stored in said memory; and
- 10 d) displaying said glucose level on said display;

15 a first electrode circuit for applying at least a first voltage, selected by said processor, between said working and counter electrodes when said test strip is inserted in said first connector, said first electrode circuit including a first digital-to-analog converter;

a second electrode circuit for applying at least a second voltage, selected by said processor, between said fill-detect electrodes when said test strip is inserted in said first connector, said second electrode circuit including a second digital-to-analog converter;

20 an auto-on circuit for developing an auto-on current through said auto-on conductor when said test strip is inserted in said first connector and for bringing said meter from a sleep mode to an active mode in response to said auto-on current; and

25 at least one analog-to-digital converter for measuring currents flowing between said working and counter electrodes and flowing between said fill-detect electrodes and for measuring an auto-on voltage drop across said auto-on conductor resulting from said auto-on current.

52. The meter of claim 51, wherein said test strip sequence comprises:

5 validating said working and counter electrodes by applying a first validation voltage between said working and counter electrodes;

10 validating said fill-detect electrodes by applying a second validation voltage between said fill-detect electrodes, while said first validation voltage is applied between said working and counter electrodes;

15 detecting said blood sample at a first location in said sample chamber by applying a drop-detect voltage between said working and counter electrodes and measuring a drop-detect current flowing between said working and counter electrodes;

detecting said blood sample at a second location in said sample chamber by applying a fill-detect voltage between said fill-detect electrodes and measuring a fill-detect current flowing between said fill-detect electrodes; and

20 after waiting an incubation time period, applying an assay voltage between said working and counter electrodes and making at least one measurement of the resulting current flowing between said working and counter electrodes.

53. A meter for use in combination with a test strip, said test strip including a working electrode, a counter electrode, a pair of fill-detect electrodes, and an auto-on conductor, said meter comprising:

20 a strip connector for receiving said test strip;

a processor;

a memory;

25 a plurality of machine instructions stored in said memory and executable by said processor for performing a test strip sequence;

a data acquisition system, controlled by said processor, for applying at least a first voltage between said working and counter electrodes and measuring any resulting current flowing between said working and counter electrodes, for applying at least a second voltage between said fill-detect electrodes and measuring any resulting current flowing between said fill-detect electrodes, and for measuring a voltage drop across auto-on conductor, when said test strip is inserted in said strip connector, said data acquisition system including at least one digital-to-analog converter and at least one analog-to-digital converter.

5 10 54. The meter of claim 53, wherein said data acquisition system includes a wake-up circuit, said wake-up circuit detecting said auto-on conductor when said test strip is inserted in said strip connector and responsively bringing said data acquisition system from a sleep mode into an active mode.

15

55. The meter of claim 53, wherein said test strip sequences comprises:
applying an assay voltage between said working and counter electrodes and making at least one measurement of the resulting current flowing between said working and counter electrodes.

20

56. The meter of claim 55, wherein said test strip sequence further comprises:
detecting said blood sample in said sample chamber by applying a fill-detect voltage between said fill-detect electrodes and measuring a fill-detect current flowing between said fill-detect electrodes.

25

57. The meter of claim 56, wherein said test strip sequence further comprises:
detecting said blood sample at a first location in said sample chamber by applying
a drop-detect voltage between said working and counter electrodes and measuring a drop-
detect current flowing between said working and counter electrodes.

5

58. A test strip for testing a blood sample, said test strip comprising:
a sample chamber for said blood sample;
a vent for venting said sample chamber;
a reagent layer disposed in said sample chamber;
at least four electrodes for measuring at least one electrical characteristic of said
blood sample in said sample chamber, said at least four electrodes including a working
electrode, a counter electrode, a fill-detect anode, and a fill-detect cathode;
a plurality of electrical contacts electrically connected to said at least four
electrodes; and
at least one auto-on electrical contact electrically isolated from said at least four
electrodes.

15

59. The test strip of claim 58, wherein said sample chamber has an opening for
receiving said blood sample.

20

60. The test strip of claim 59, wherein said sample chamber is dimensioned to
draw said blood sample in through said opening by capillary action.

61. The test strip of claim 60, wherein said test strip has a proximal end and a
distal end, said first opening being located at said proximal end.

62. The test strip of claim 61, wherein said proximal end is narrower than said distal end.

5 63. The test strip of claim 58, further comprising:
a dielectric layer having a slot therein, said slot defining said sample chamber.

64. The test strip of claim 63, wherein said slot further defines said vent.

10 65. The test strip of claim 64, wherein said slot has a wide portion and a narrow portion, said wide portion defining said sample chamber, said narrow portion defining said vent.

15 66. The test strip of claim 63, further comprising:
an adhesive layer disposed on said second dielectric layer, said adhesive layer having a break therein extending from said slot.

67. The test strip of claim 66, wherein said break in said adhesive layer defines
said vent.

20

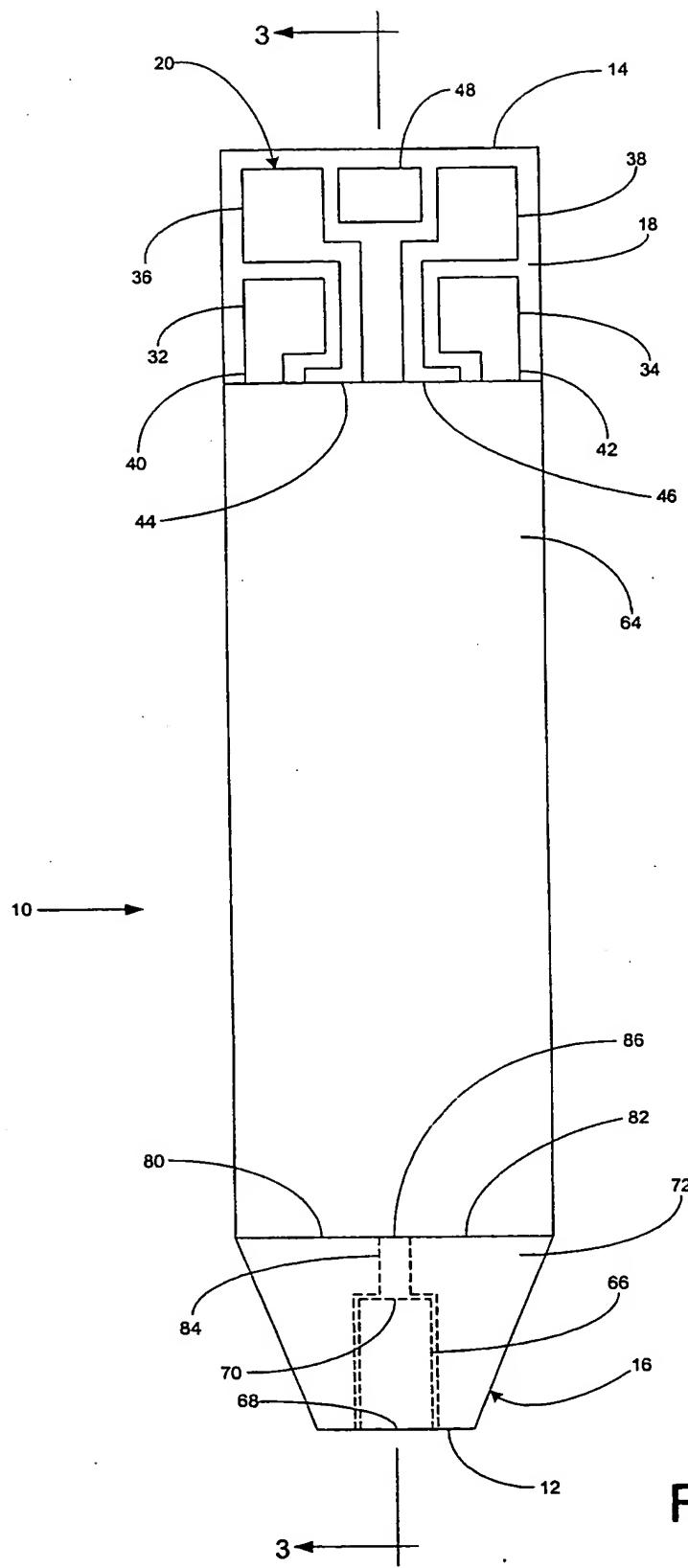


FIG. 1

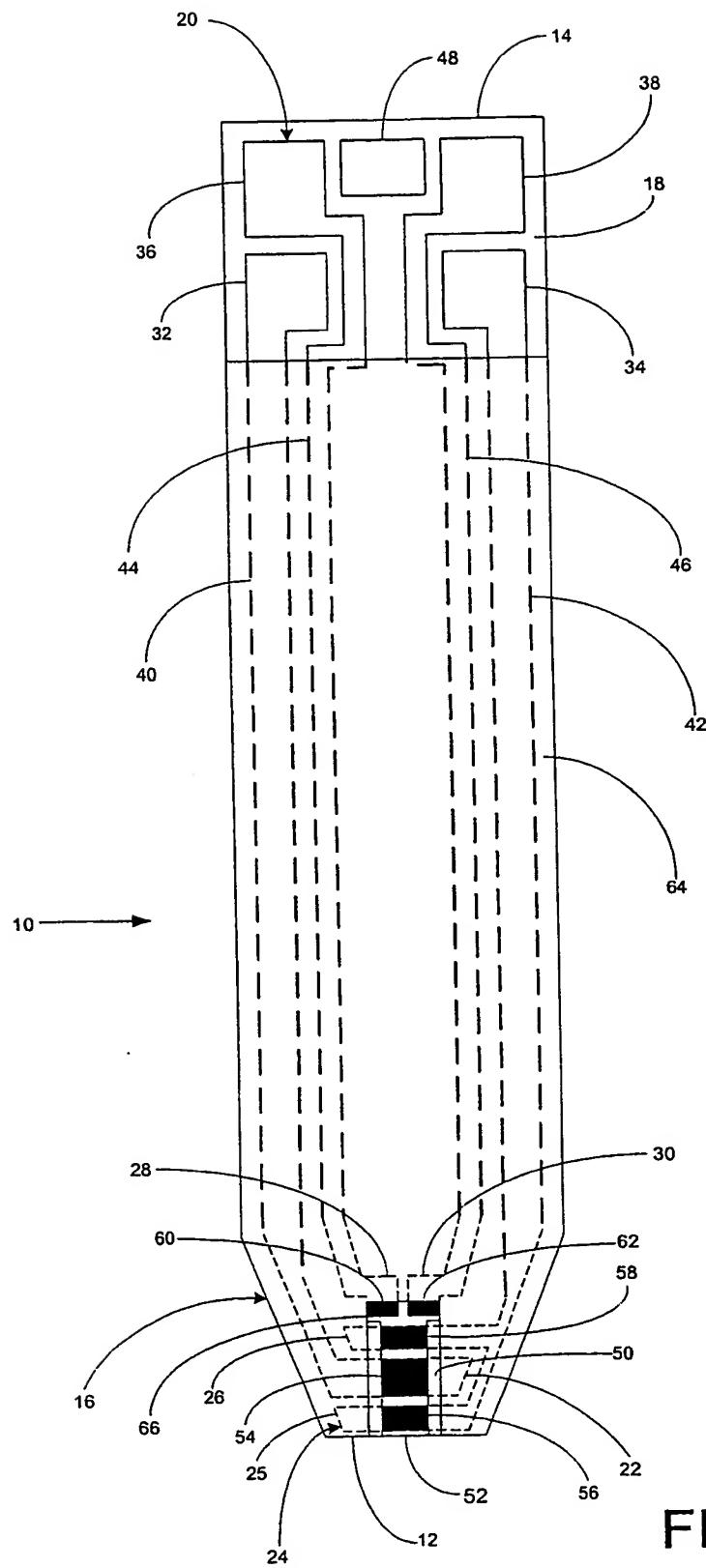


FIG. 2

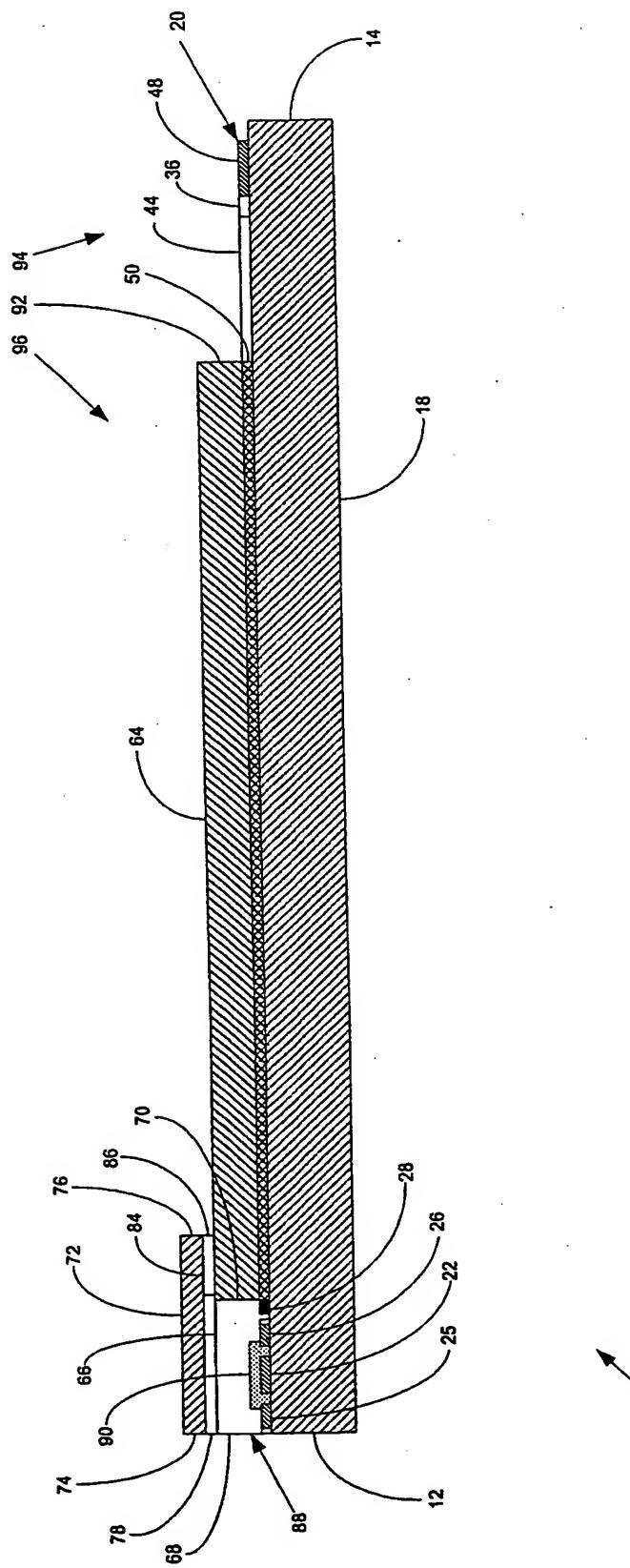


FIG. 3

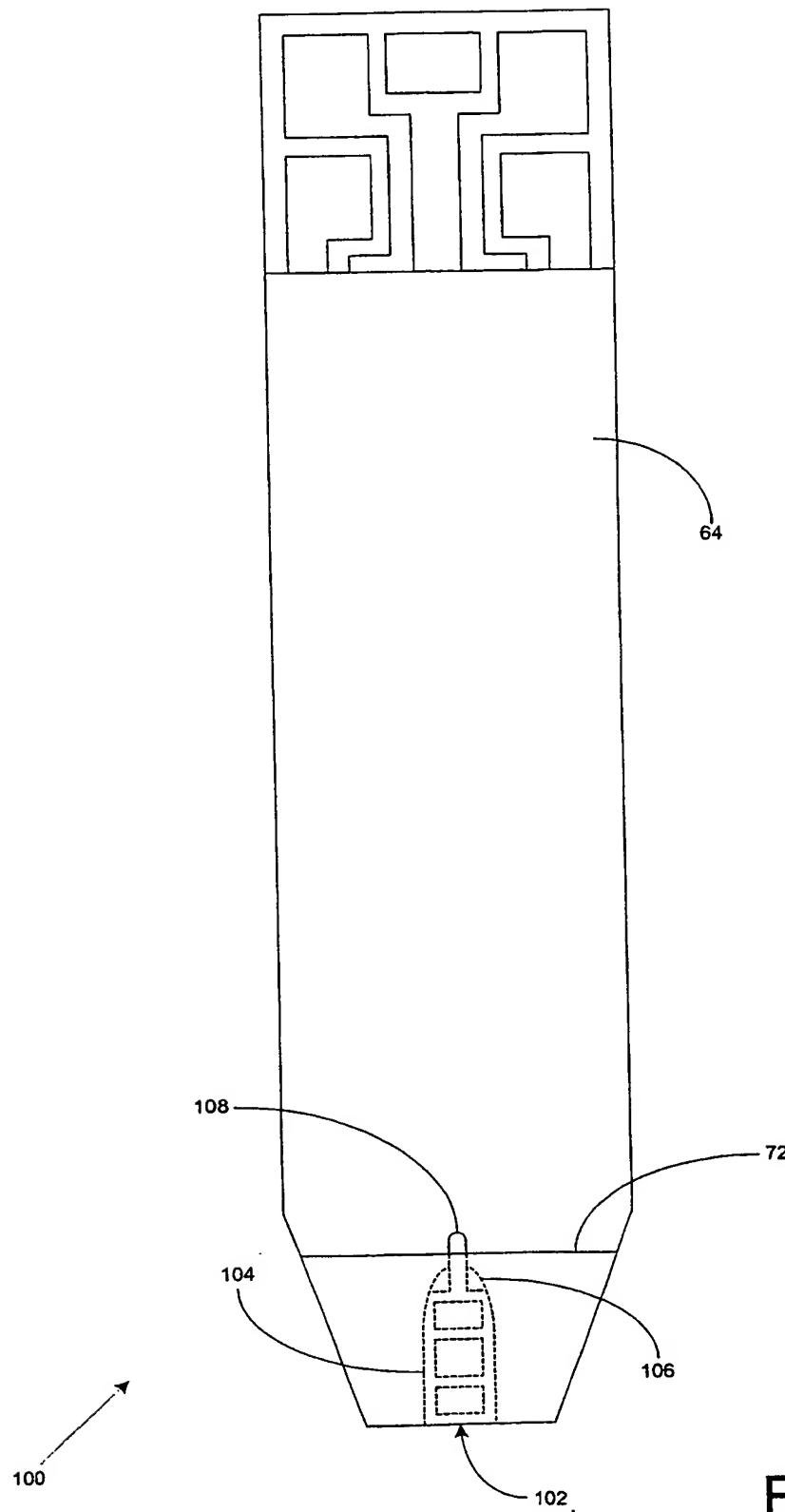


FIG. 4

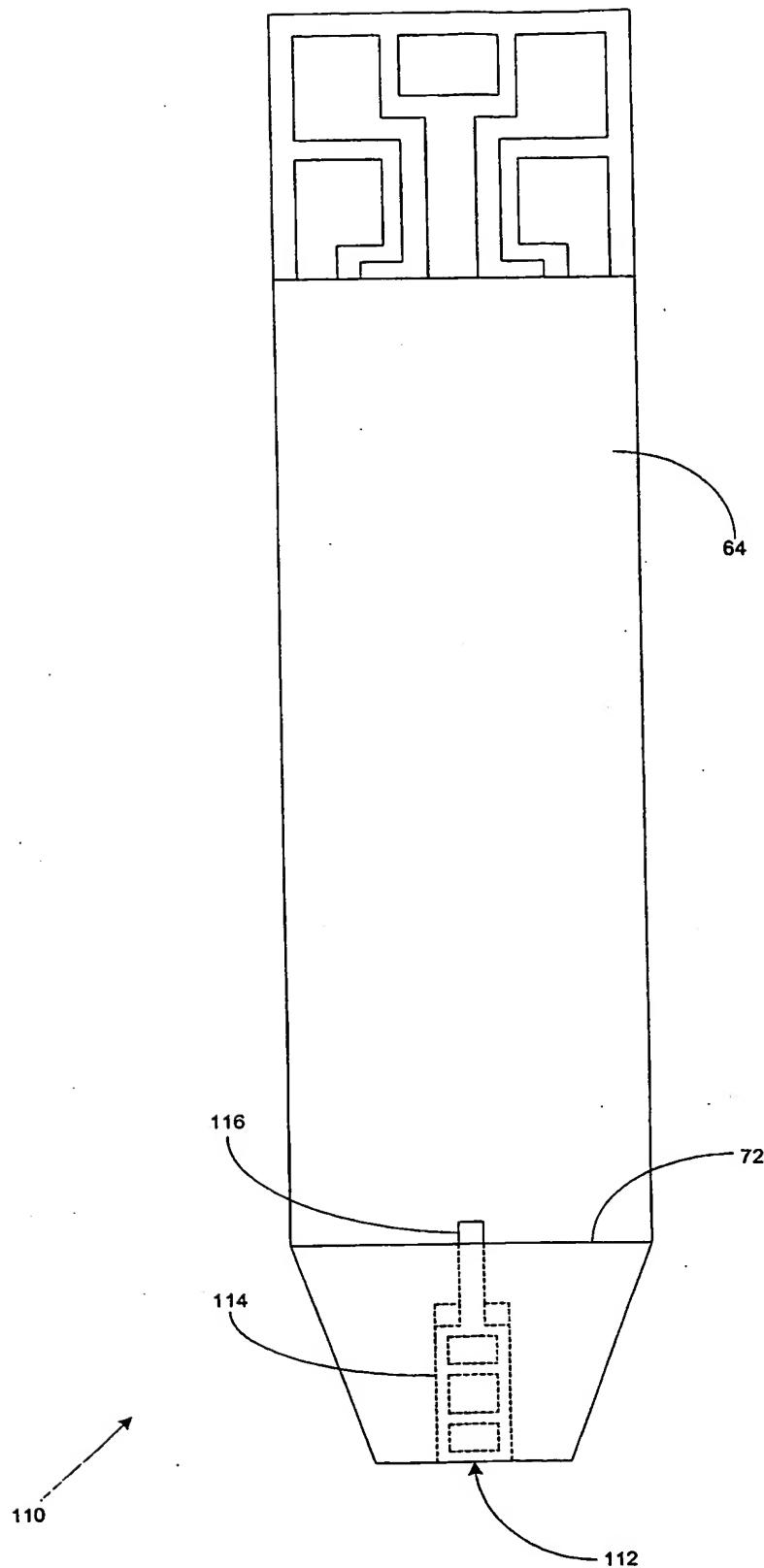


FIG. 5

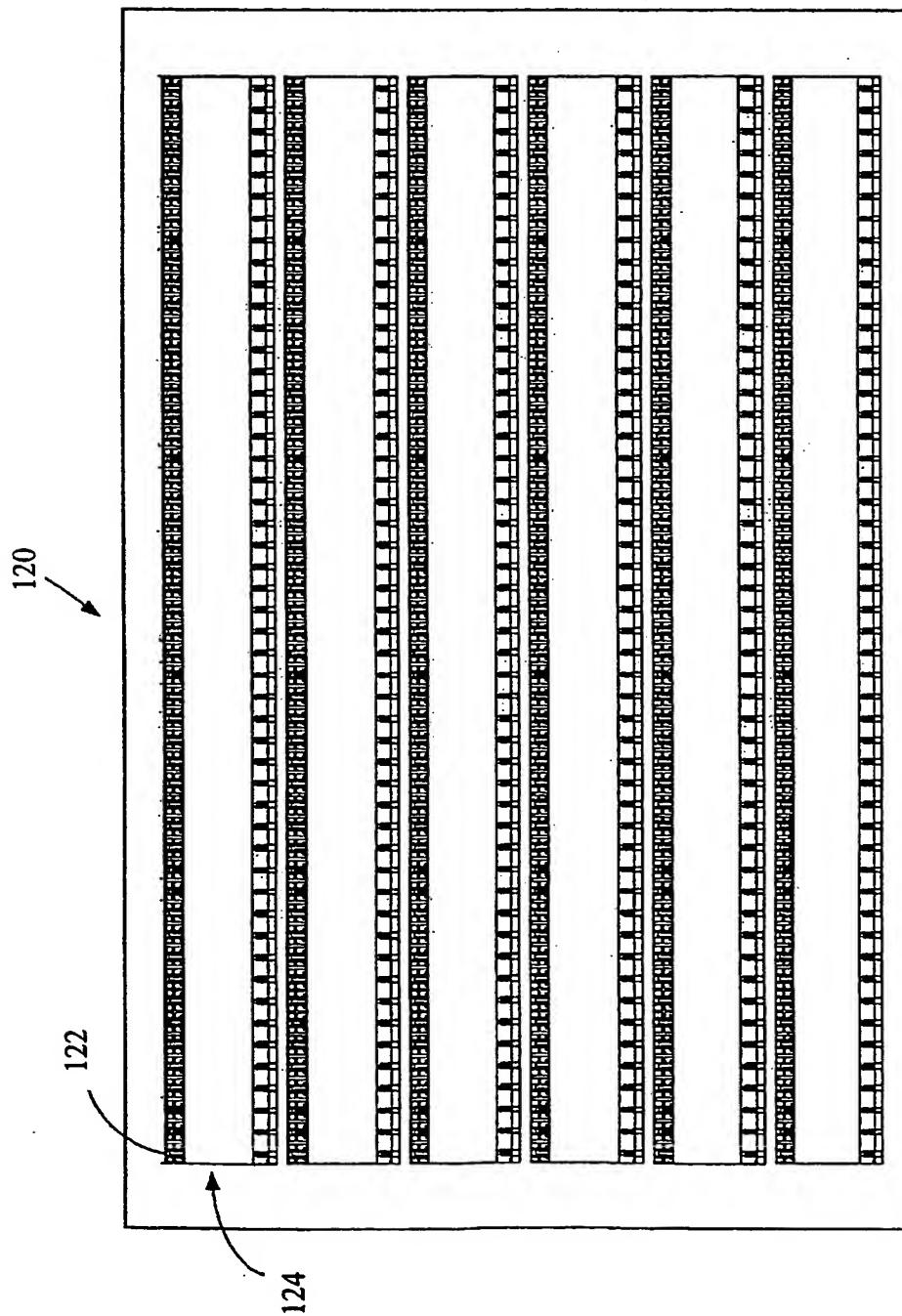
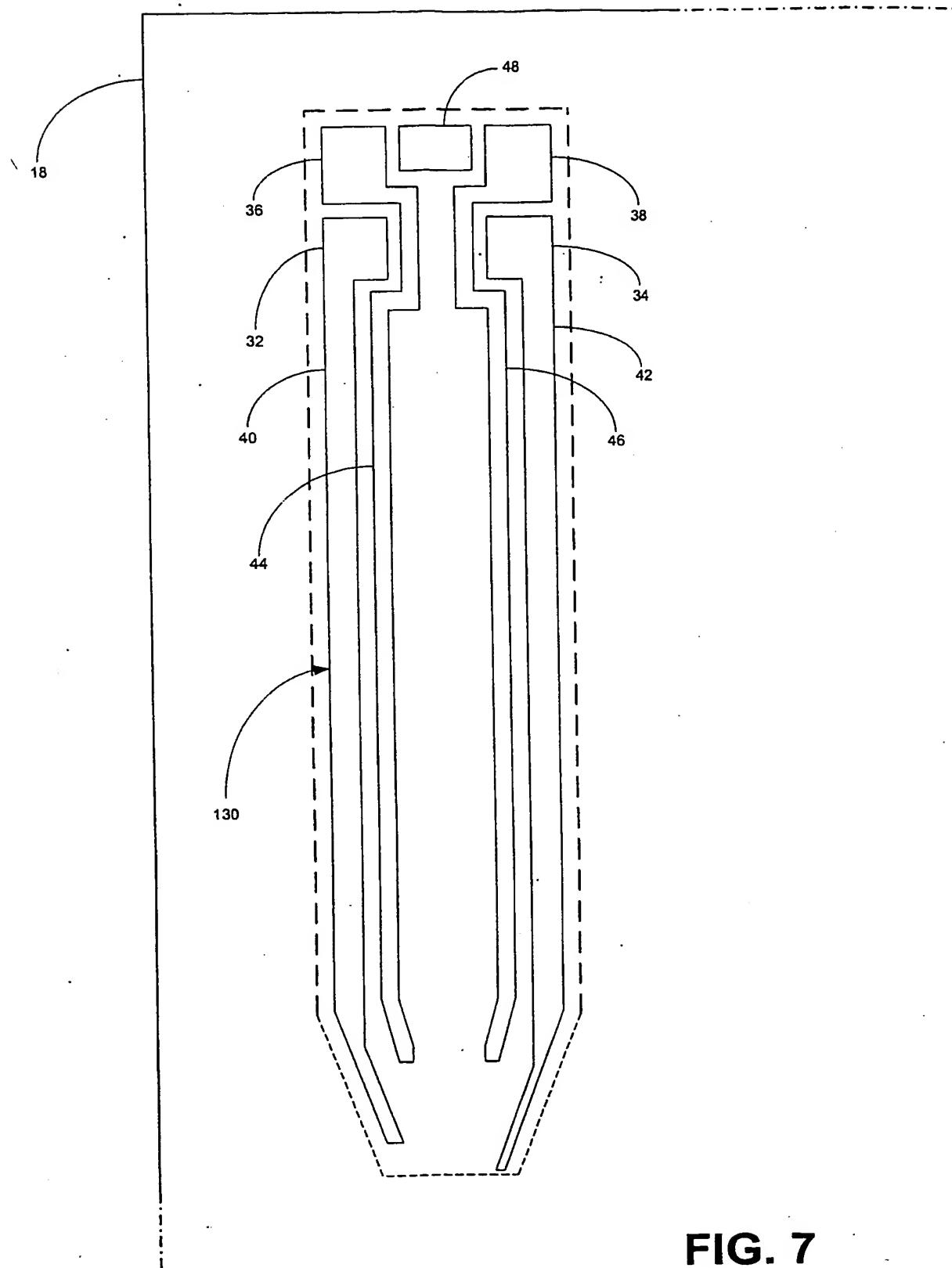
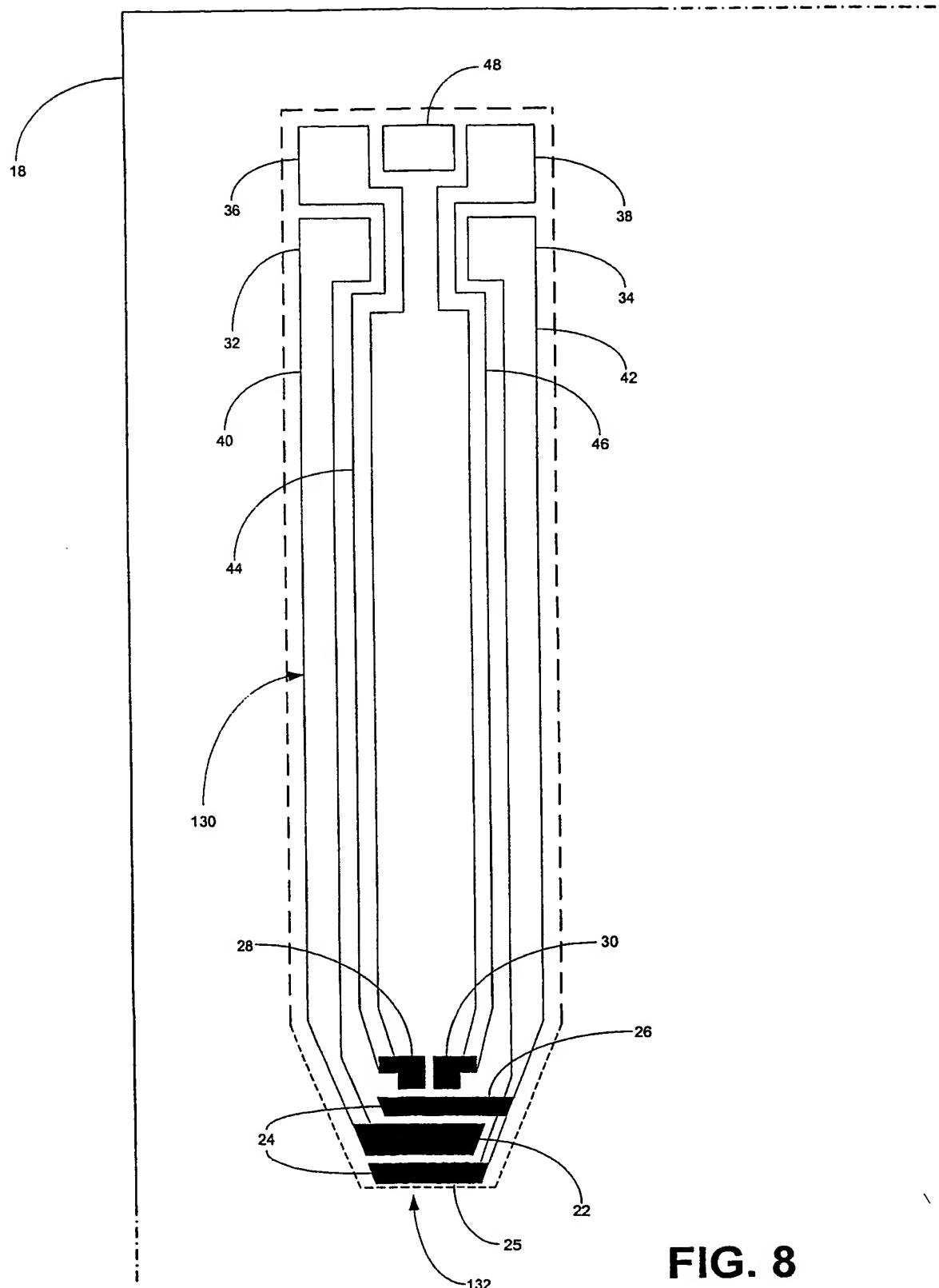
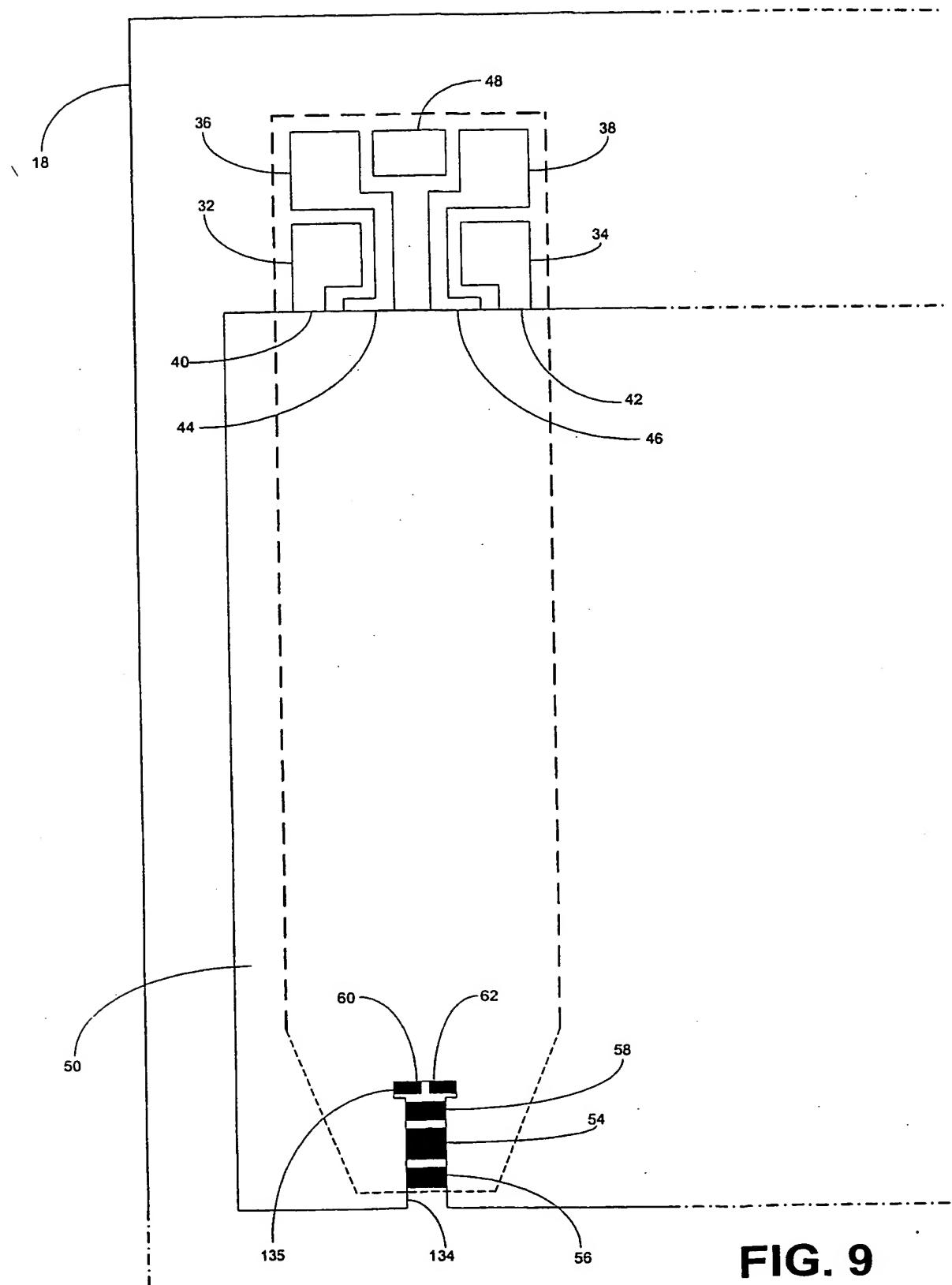
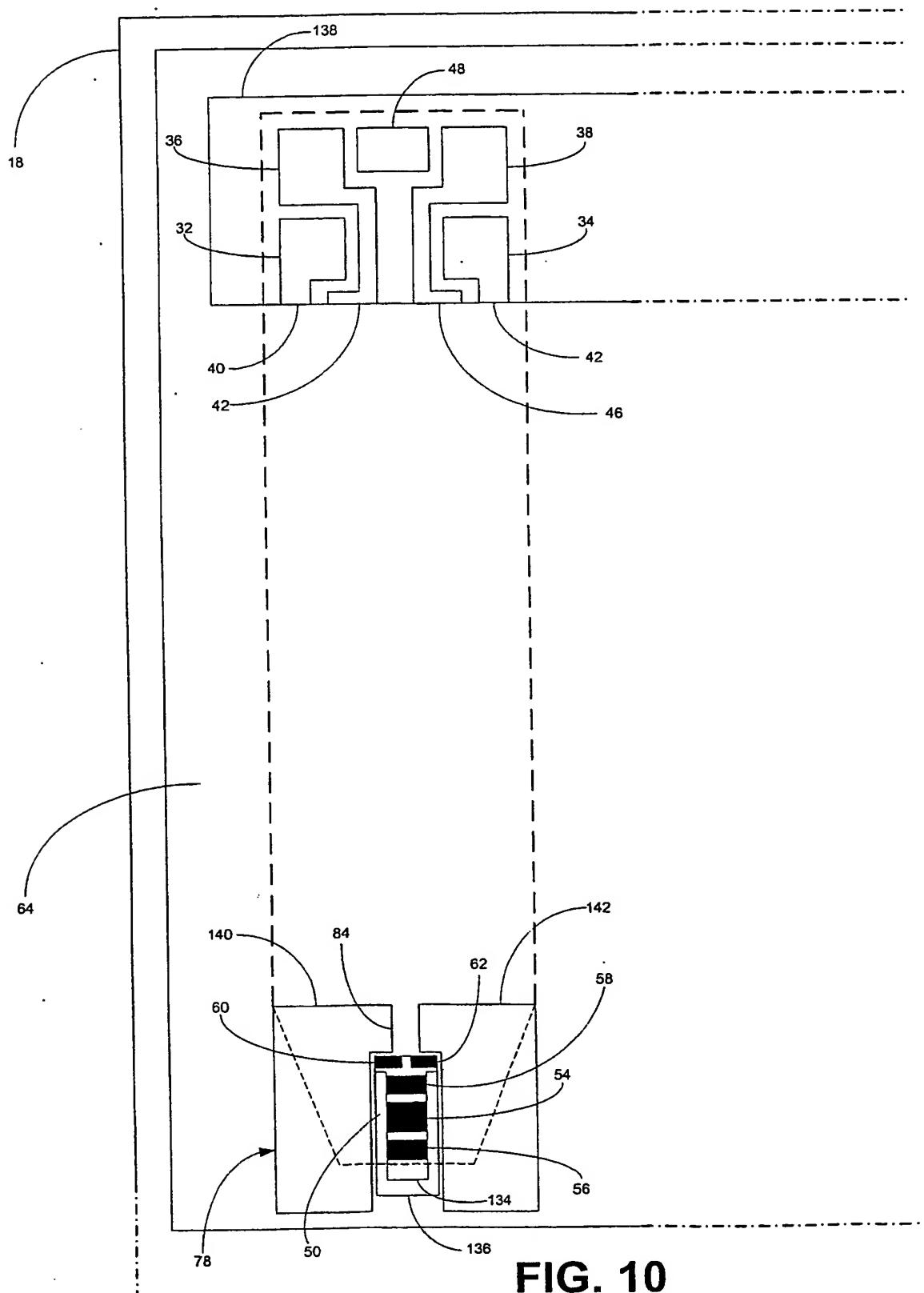


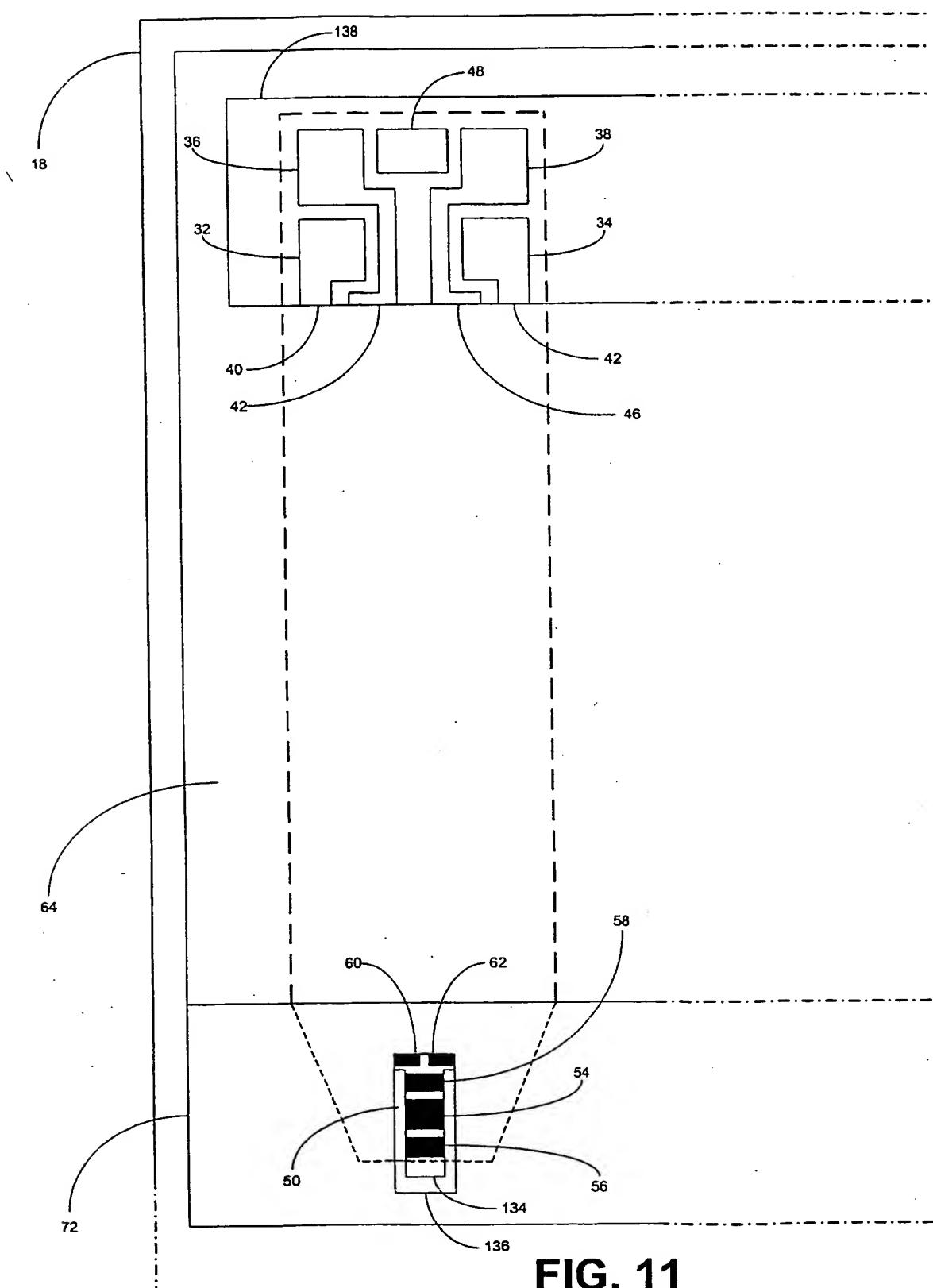
FIG. 6

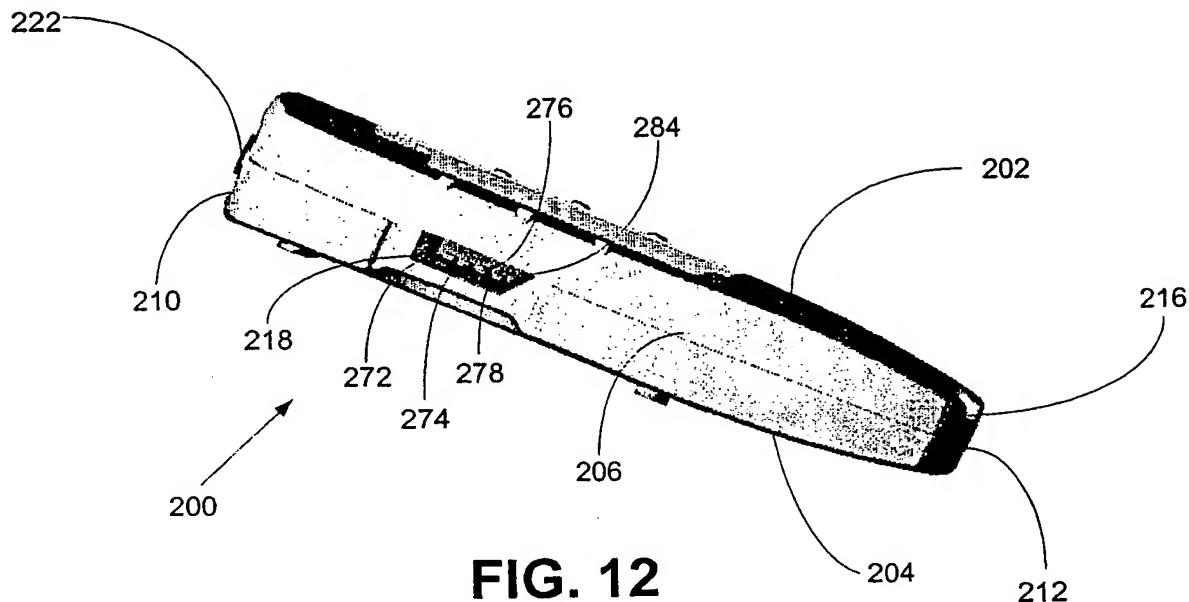
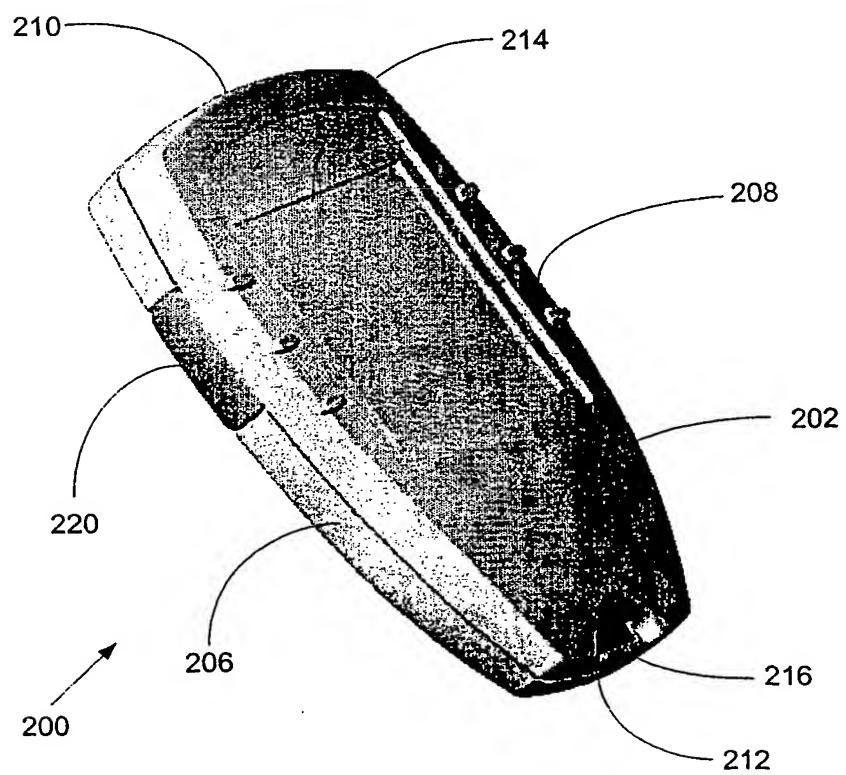
**FIG. 7**

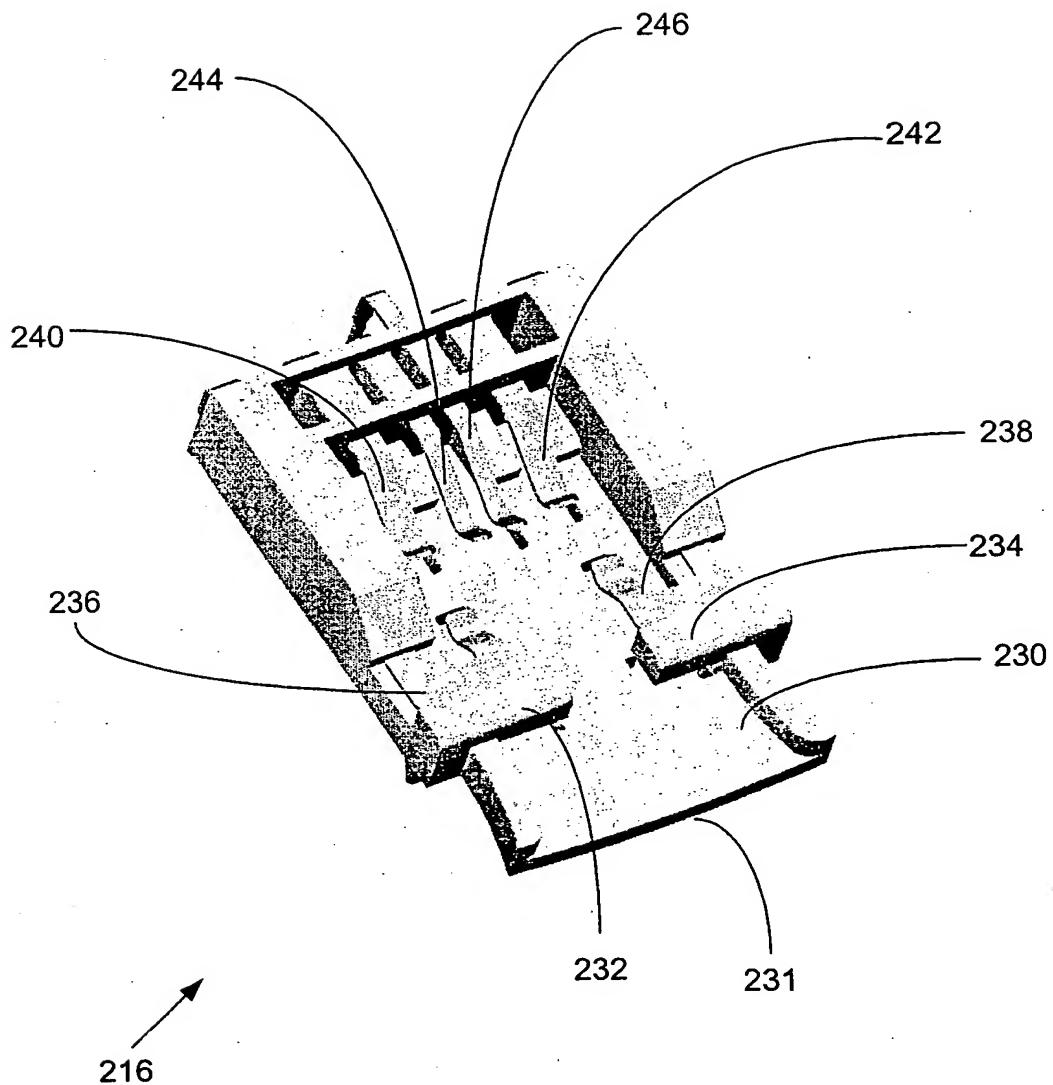
**FIG. 8**

**FIG. 9**



**FIG. 11**

**FIG. 12****FIG. 13**

**FIG. 14**

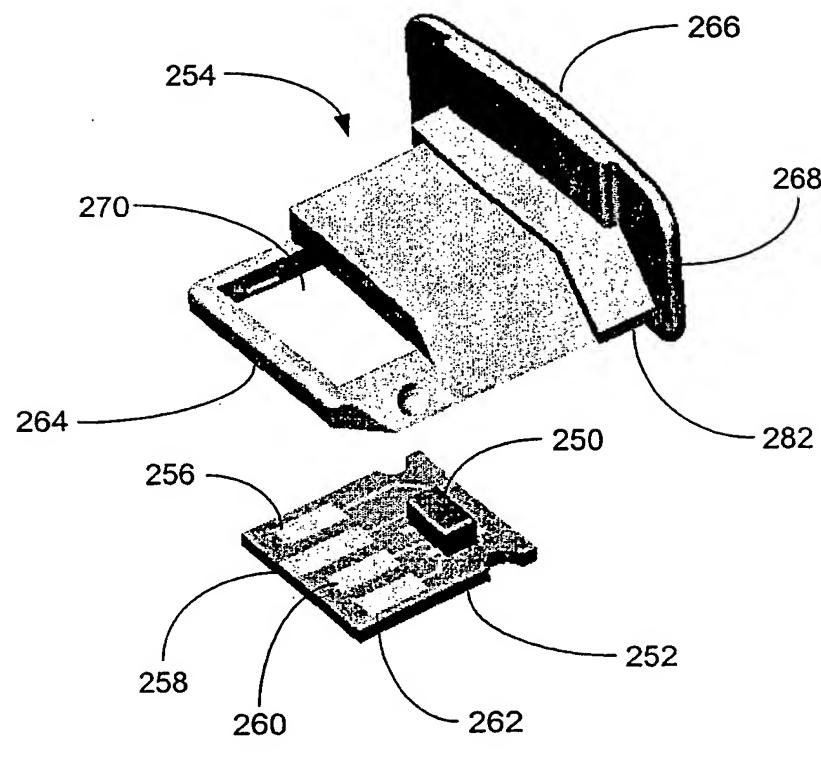


FIG. 15

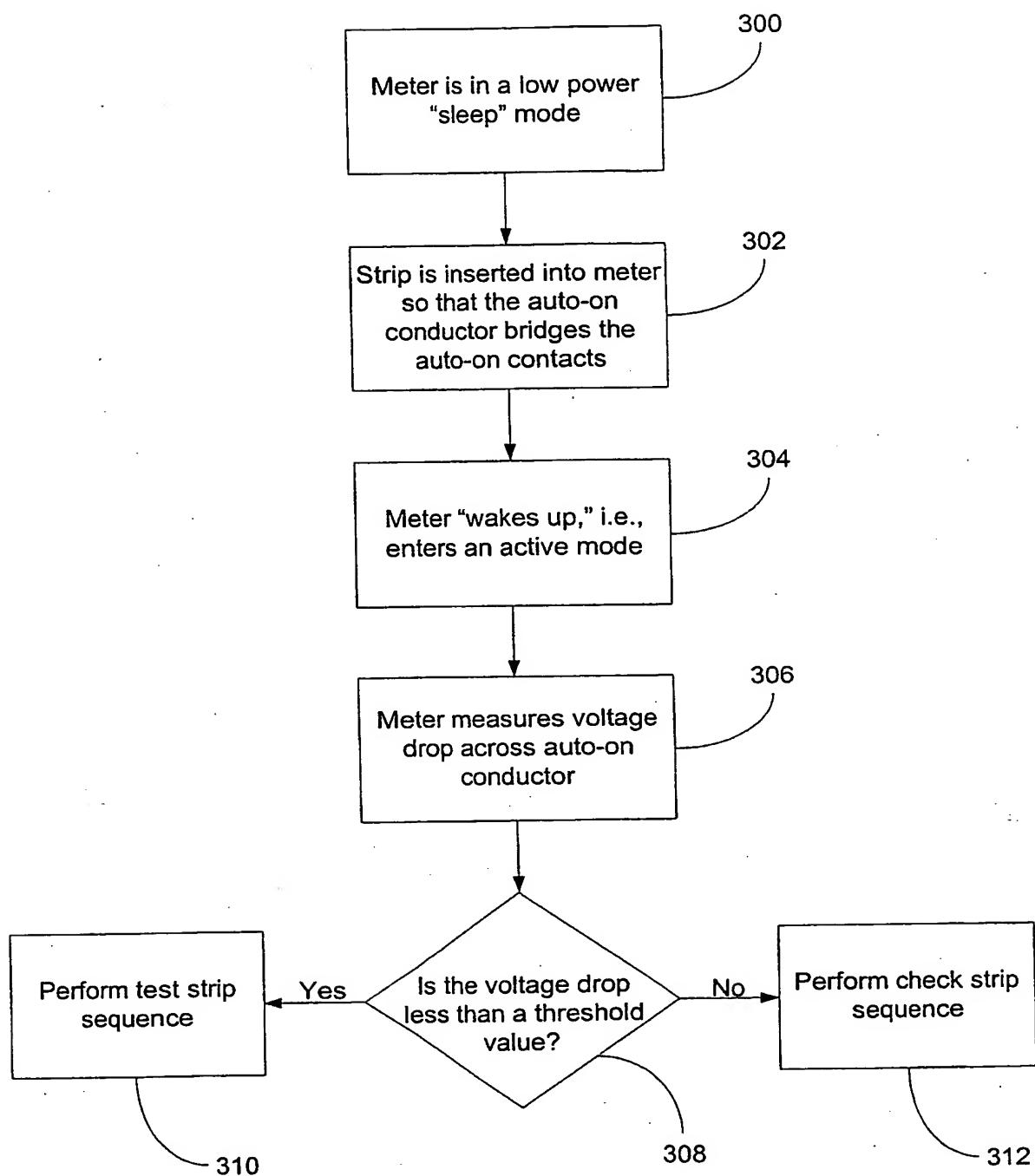


FIG. 16

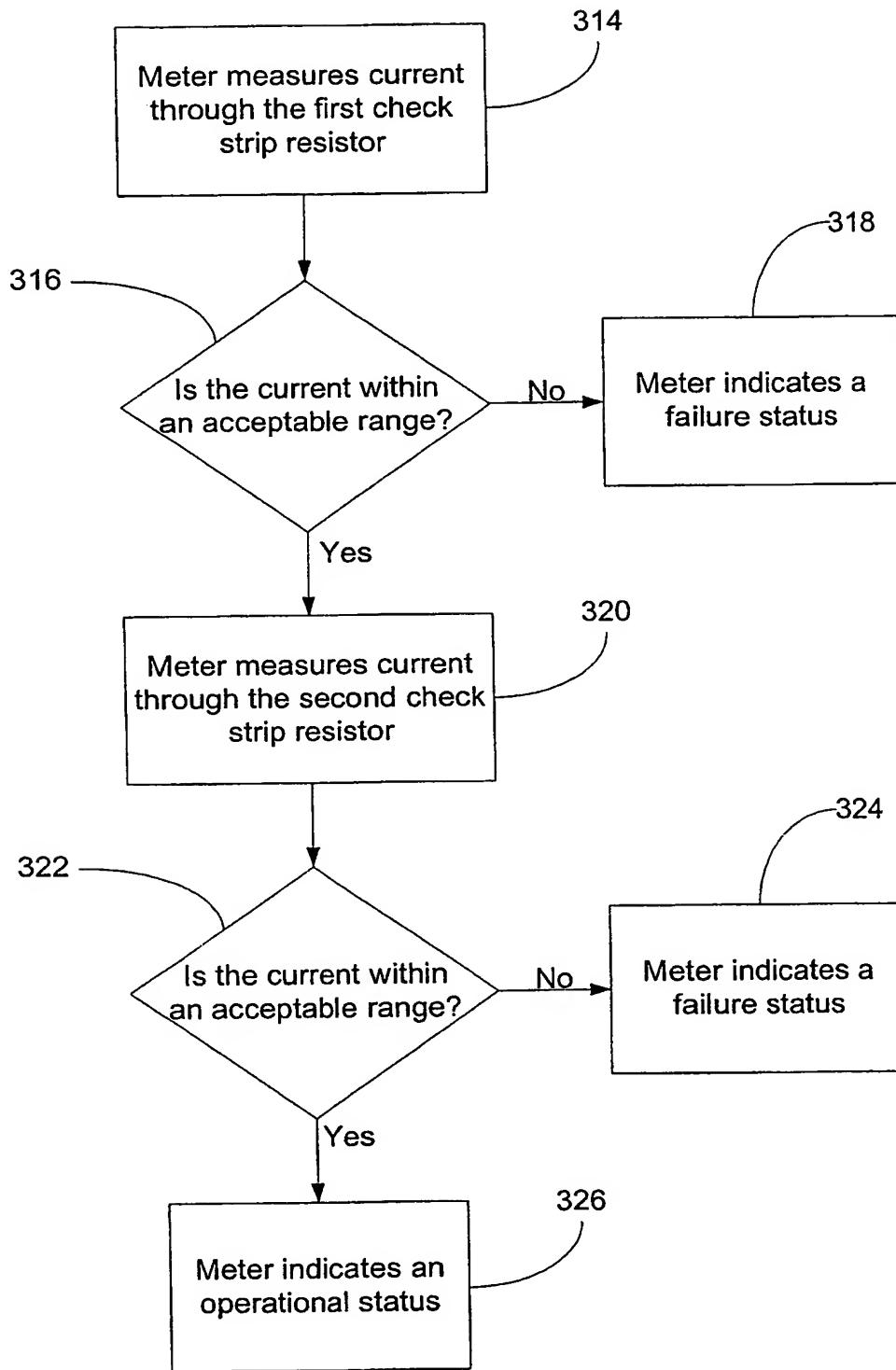


FIG. 17

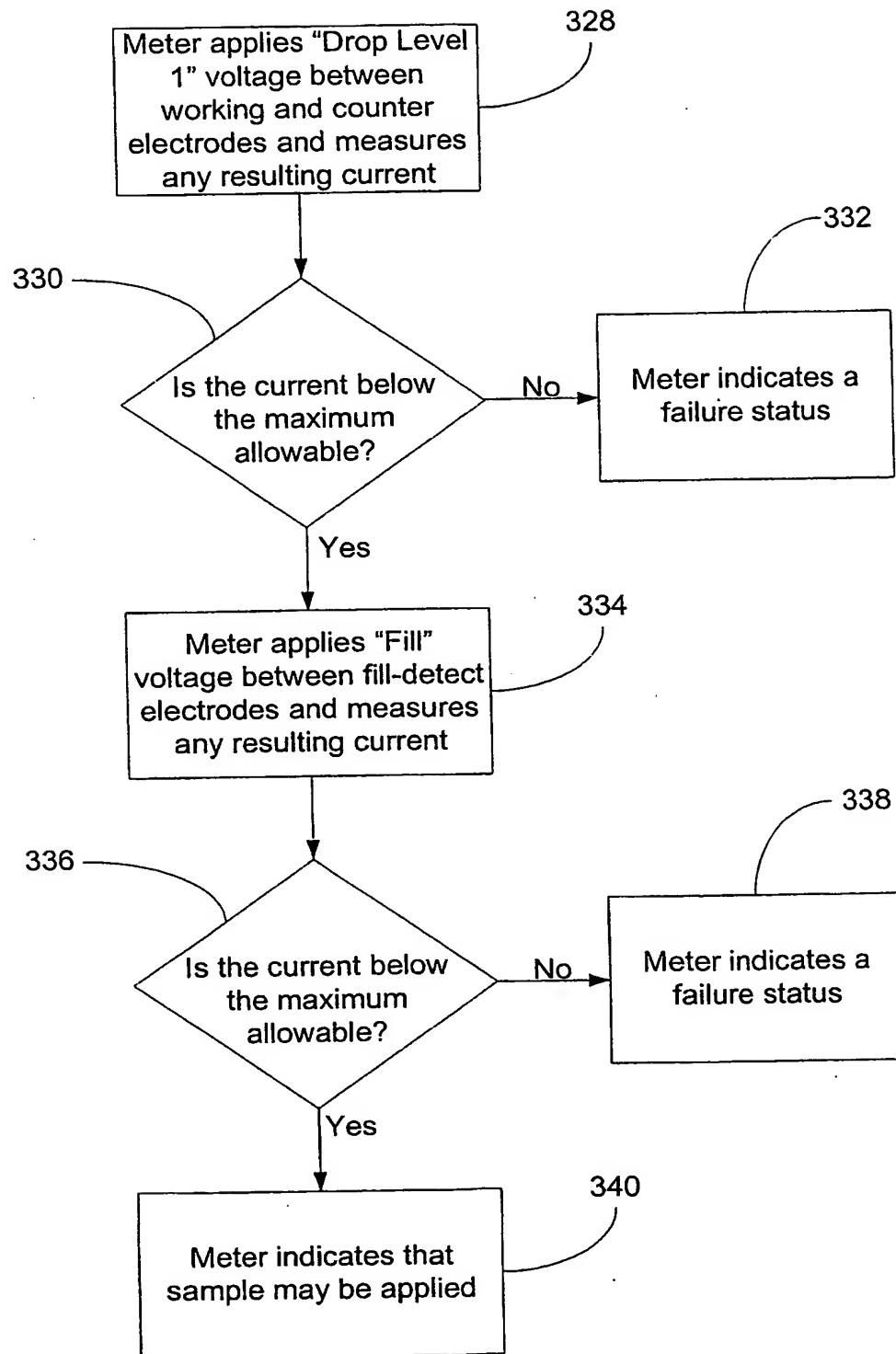


FIG. 18

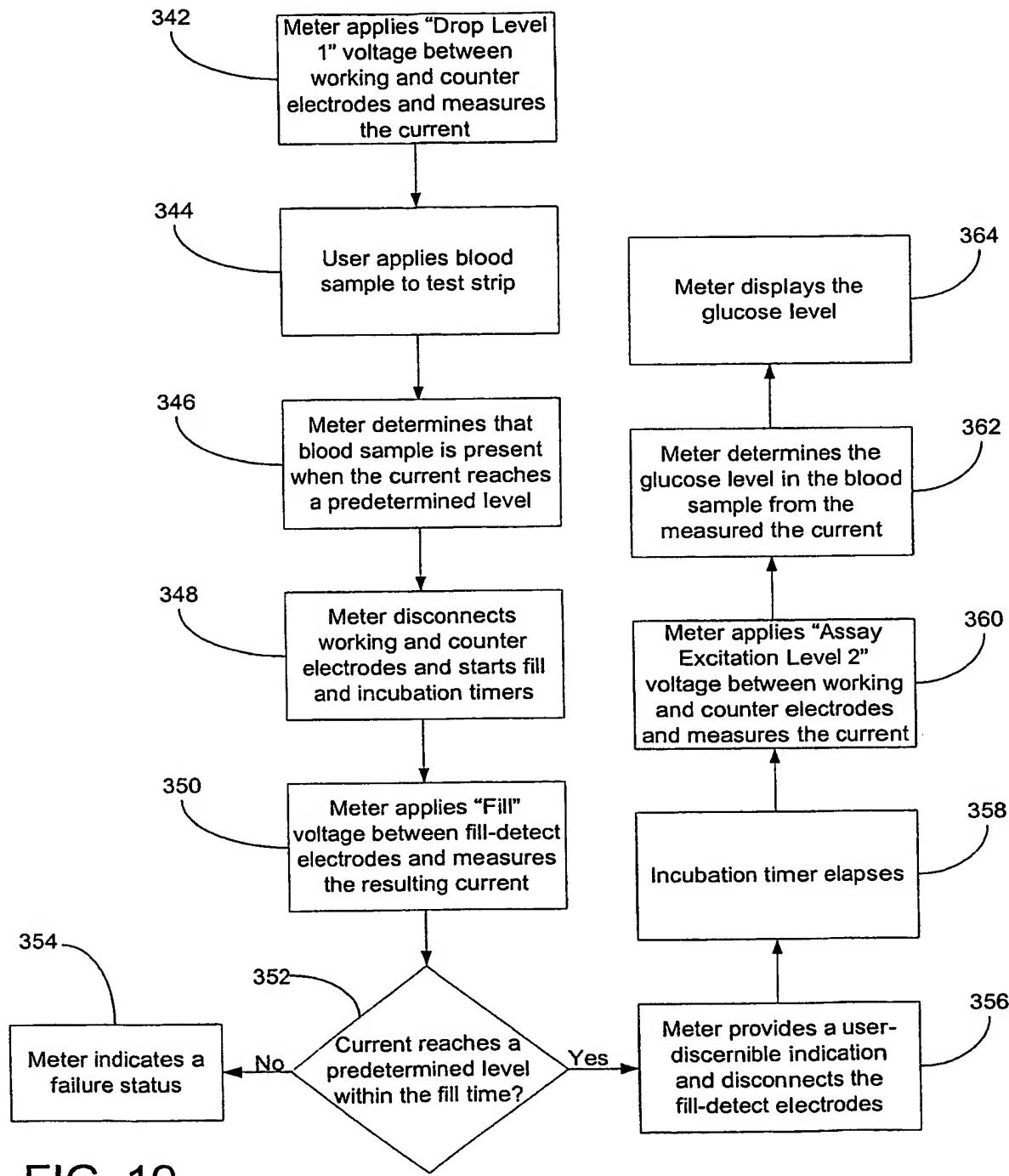
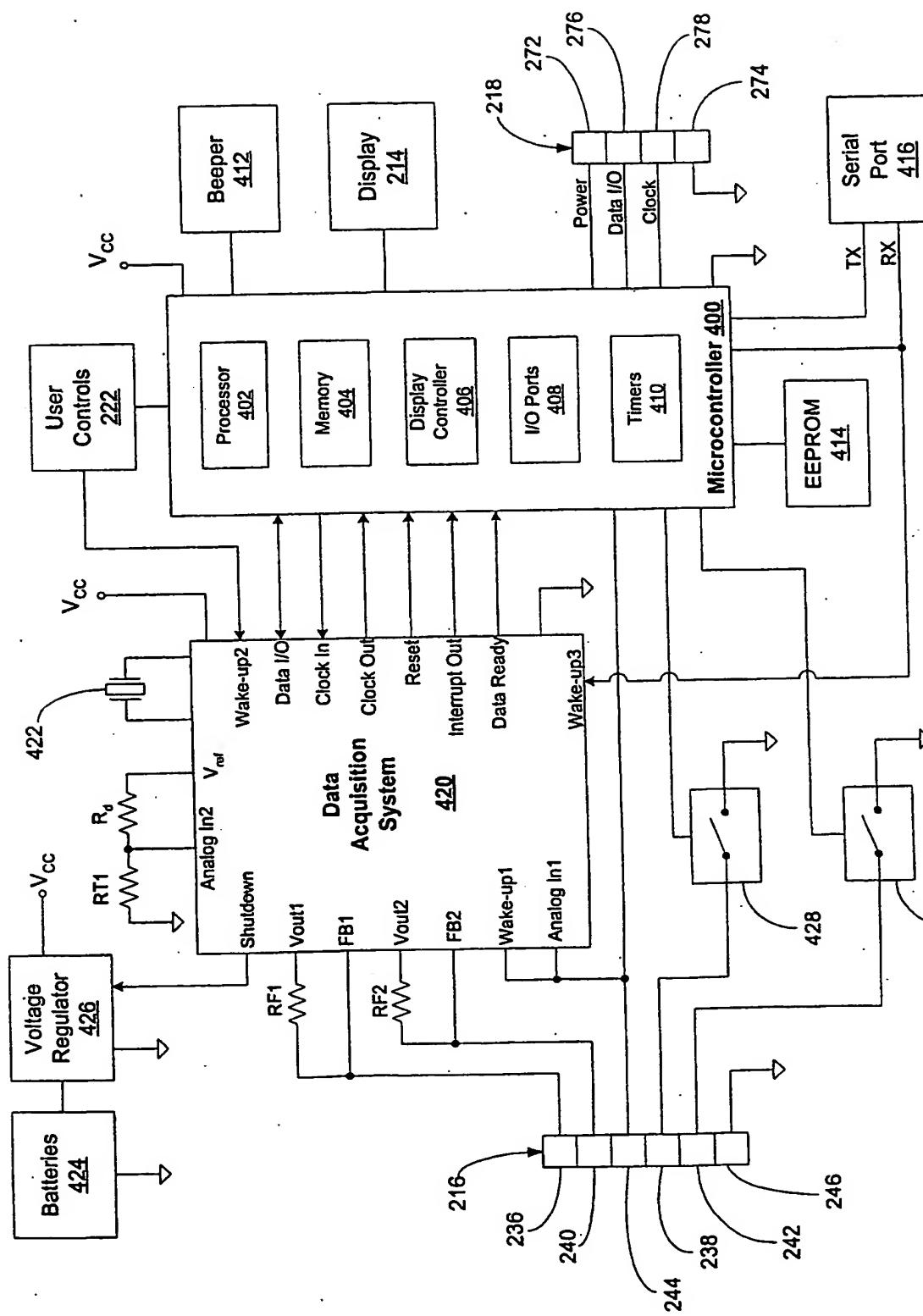
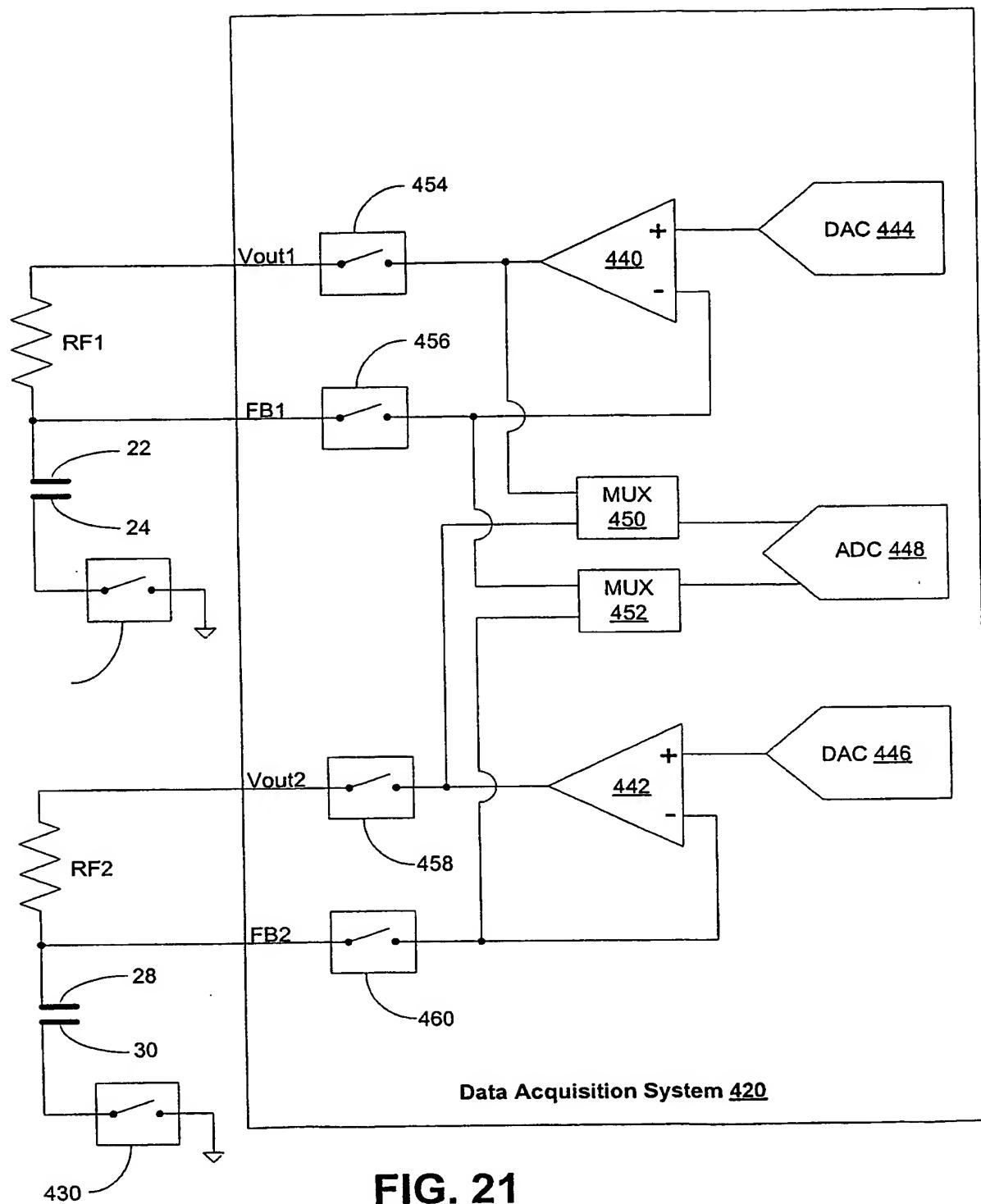


FIG. 19

**FIG. 20**

**FIG. 21**

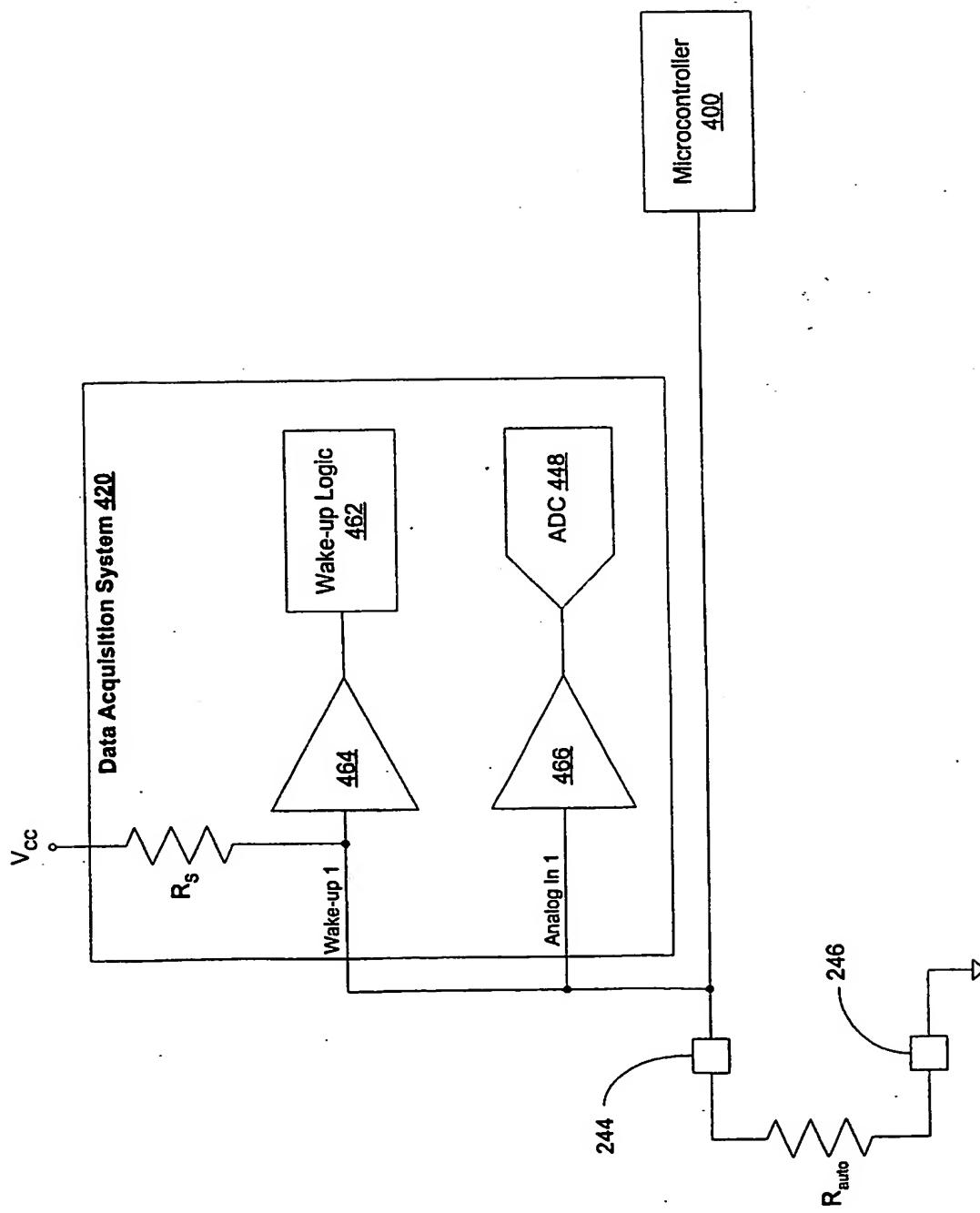


FIG. 22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/12899

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 27/00, 33/66
 US CL : 436/ 95, 149, 150; 422/82.01, 82.02; 435/14; 204/403.01, 403.02, 403.04, 403.10, 403.11; 702/19, 32
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/63, 95, 149, 150; 422/82.01, 82.02; 435/14; 204/403.01, 403.02, 403.04, 403.10, 403.11; 702/19, 31, 32

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,120,420 A (NANKAI et al) 09 June 1992, abstract, figures 4, 6 and 12, column 4, lines 50-68, column 5, lines 1-29 and column 9, lines 30-54.	1-24, 58-67
---		-----
A		25-57
Y, P	US 2002/0084196 A1 (LIAMOS et al.) 04 July 2002, paragraphs nos. 0139-0147.	1-24, 58-67
---		-----
A		25-57
Y	US 5,925,021 A (CASTELLANO et al.) 20 July 1999, column 14, lines 40-67 and column 15, lines 1-32.	1-24, 58-67
---		-----
A		25-57
Y, P	US 2002/0157947 A1 (RAPPIN et al.) 31 October 2002, paragraph nos. 0014 and 0040-0055.	1-24, 58-67
---		-----
A		25-57
A, P	US 2003/0036202 A1 (TEODORCYZK et al.) 20 February 2003, paragraph nos. 0056-0062.	39-41

Further documents are listed in the continuation of Box C.

See patent family annex.

Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

30 July 2003 (30.07.2003)

Date of mailing of the international search report

18 AUG 2003

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Maureen Wallenhorst

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P\	US 6,413,213 B1 (ESSENPREIS et al.) 02 July 2002, column 1, lines 23-45, column 3, lines 48-60 and column 4, lines 35-55.	42-57
A	US 6,377,894 B1 (DEWEESE et al.) 23 April 2002, column 2, lines 28-41, column 4, lines 27-49, column 5, lines 53-67 and column 6.	42-50
A	WO 01/73124 A2 (DAVIES et al.) 04 OCTober 2001, whole document.	1-67
A	WO 01/71328 A1 (RYU et al.) 27 September 2001, whole document.	1-24, 51-67
A	US 6,241,862 B1 (McAleer et al.) 05 June 2001, whole document.	1-24, 58-67
A	US 5,989,917 A (McAleer et al.) 23 November 1999, whole document.	42-57
A	US 5,762,770 A (PRITCHARD et al.) 09 June 1998, whole document.	1-24, 58-67
A	US 5,264,103 A (YOSHIOKA et al.) 23 November 1993, whole document.	1-24, 58-67

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/12899

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/12899

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-24 and 58-67, drawn to a test strip for testing a blood sample for glucose and a method for making.

Group II, claim(s) 25-38, drawn to a method of measuring glucose in a blood sample using both a test strip and a meter.

Group III, claim(s) 39-41, drawn to a method of test strip identification.

Group IV, claim(s) 42-50, drawn to a removable data storage device for a meter.

Group V, claim(s) 51-57, drawn to a meter for use with a test strip to measure glucose.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The invention in Group I includes the special technical features of first and second insulating sheets, first and second dielectric layers and an adhesive layer, which the inventions in Groups II-V lack. The invention in Group II includes a test strip for measuring glucose, but does not have the special technical features of the test strip in Group I, as mentioned above. The invention in Group III includes the special technical feature of determining if a test strip inserted into a meter is a test strip containing a sample or a quality control strip for calibration, which the inventions in Groups I, II, IV and V lack. The invention in Group IV includes the special technical feature of a circuit board for data storage on a carrier, which the inventions in Groups I, II, III and V lack. The invention in Group V includes the special technical feature of measuring glucose in a test sample on a test strip using a meter having a removable data storage device, a processor, a memory, a display and machine language instructions, which the inventions in Groups I, II, III and IV lack. Specifically, the invention in Group IV lacks the machine language instructions included in the invention of Group V. The invention in Group II includes a meter for reading a test strip, but does not have the special technical features of the meter in Group V, such as the processor, memory and machine language instructions.

Continuation of B. FIELDS SEARCHED Item 3:

EAST/USPAT, PGPUB; WEST/JPO, EPO, DERWENT; STN/CAPLUS, CAOLD, MEDLINE, BIOSIS
search terms: blood, glucose, test strip, meter, electrodes, dielectric, data storage, fill-detect, auto-on

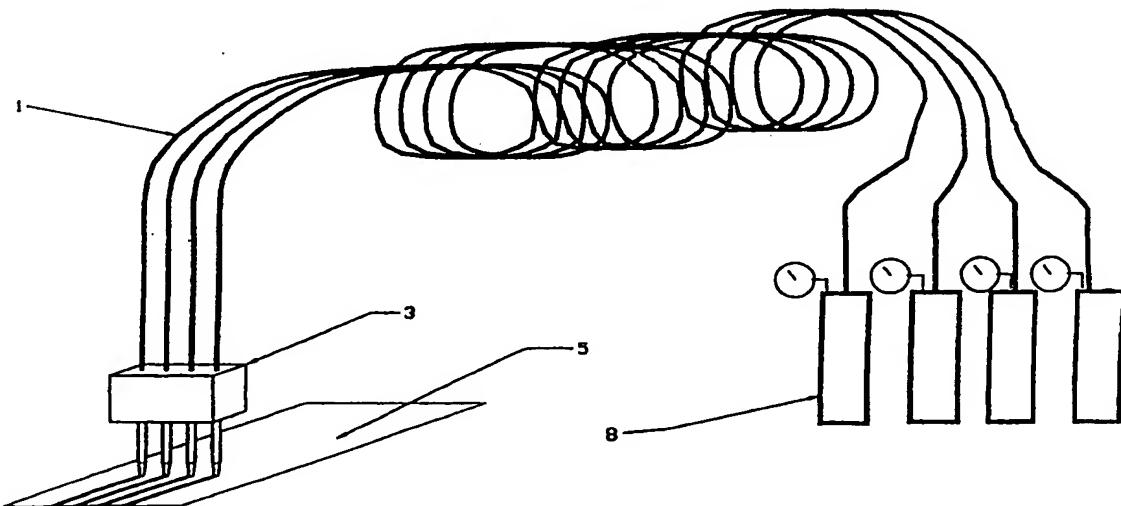
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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G01N 33/52, C12Q 1/26 // B05C 5/02	A1	(11) International Publication Number: WO 98/30904 (43) International Publication Date: 16 July 1998 (16.07.98)
(21) International Application Number: PCT/US98/00477		
(22) International Filing Date: 8 January 1998 (08.01.98)		
(30) Priority Data: 60/034,668 9 January 1997 (09.01.97) US		
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/034,668 (CON) Filed on 9 January 1997 (09.01.97)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(71) Applicant (for all designated States except US): MERCURY DIAGNOSTICS, INC. [US/US]; Suite D, 1137 San Antonio Road, Palo Alto, CA 94303 (US).		Published With international search report.
(72) Inventors; and		
(75) Inventors/Applicants (for US only): DOUGLAS, Joel, S. [US/US]; 2048 Calabazas Boulevard, Santa Clara, CA 95051 (US). GLEISNER, John, M. [US/US]; 20504 52nd Avenue West, Lynnwood, WA 98036 (US).		
(74) Agents: DILLAHUNTY, T., Gene et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).		

(54) Title: METHODS FOR APPLYING A REAGENT TO AN ANALYTICAL TEST DEVICE



(57) Abstract

This invention provides methods and apparatus for applying a reagent to an analytical test device. The methods and apparatus employ a nozzle and a flexible restrictor to accurate control the amount of reagent applied to the test device. The analytical test devices prepared by the methods of this invention are used to determine the presence or the quantity of an analyte in a liquid sample, such as whole blood.

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METHODS FOR APPLYING A REAGENT TO AN ANALYTICAL TEST DEVICE

5

BACKGROUND OF THE INVENTION

Field of Invention

This invention relates to improved methods for applying a reagent to an analytical test device. The test devices prepared by the methods of this invention are typically used to determine the presence and/or the quantity of an analyte in a liquid test sample, such as whole blood. This invention also provides apparatus for applying the reagent to the analytical test device.

State of the Art

Analytical test devices containing a reagent are commonly used to determine the presence or the quantity of a particular analyte in liquid samples, such as whole blood. For example, diabetics typically use such test devices to monitor the level of glucose in their blood. The reagent on the test device typically indicates the presence or the quantity of the analyte in the liquid sample using either spectrophotographic, color match or electrochemical technology. Such test devices generally comprise a substrate, such as a non-porous handle, and an absorbent test pad attached to the handle. The reagent is typically applied to the test pad either before or after assembly and then dried to create a "dry" chemical test device.

25

-2-

Numerous methods of applying reagents and coatings to analytical test devices have been described in the literature. These methods include dip coating, roll coating, ink jet application, screen printing, brushing, painting and the like.

5 For example, Bertek, Inc. literature entitled "The Technology of Coating and Laminating" (1986) describes various coating technologies and techniques, including roll coating, knife over roll and slot coating methods. These methods typically apply the reagents either across the whole web of the test device or in a continuous manner.

10

Similarly, U.S. Patent 5,547,702 to Gleisner, describes a method of applying a reagent mixture down a reagent test pad in a continuous manner.

15 Many other patents describe imbibing processes such as dip coating processes. For example, U.S. Patent 4,935,346 to Phillips et al., describes a process in which a membrane is dip coated and then dried.

20 When the test devices prepared by such methods are used to determine the quantity of an analyte in a liquid sample, it is particularly important that the amount of reagent deposited on the test device be accurately controlled so that reproducible test results are achieved. Additionally, the reagents employed in the test devices are often expensive and need to be conserved. Therefore, it is particularly important that the reagent be applied to the test device only where it is needed. Accordingly, it would highly desirable to develop novel methods and apparatus for applying the reagent to the test device such the reagent is deposited on the test device in an accurate and controlled manner.

25
30

SUMMARY OF THE INVENTION

The present invention provides improved methods and apparatus for applying a reagent to an analytical test device. The methods and apparatus of this invention employ flexible restrictors to accurately control the amount of reagent applied to the test device. Such restrictors allow the reagent to be applied to the test device in a predetermined amount thereby providing reproducible test results. Applying the reagent with such restrictors also allows the reagent to be applied only where it is needed thus conserving expensive reagents.

10

Accordingly, in one of its method aspects, the present invention provides a method for applying a reagent to a test device comprising:

- (a) providing a test device comprising a substrate and a test pad attached to the substrate;
- 15 (b) providing a fluid delivery system comprising a nozzle and a flexible restrictor attached to the nozzle for delivery of a reagent from the nozzle to the test pad;
- (c) applying a reagent comprising an indicator system and an oxidase enzyme or a peroxidase enzyme in a predetermined amount and at a 20 predetermined pressure through the nozzle and the flexible restrictor to the test pad.

In a preferred embodiment of this invention, the fluid delivery system further comprises a pressure delivery system. The pressure delivery system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

In another preferred embodiment, the fluid delivery system further comprises a positive displacement system. The positive displacement system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

-4-

In still another preferred embodiment, a brush is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad. In this embodiment, the brush applies or paints the reagent onto the test pad. In addition to applying the reagent more evenly on the test
5 pad, the brushes also provide additional damping of any pulsation from the pumping system.

The reagent can be applied to the test pad continuously or in a discrete amount. Accordingly, in a preferred embodiment of this invention, the reagent is applied to the test pad in a metered amount continuously down the length of the pad. When the reagent is applied continuously to the test pad, the nozzle preferably has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches. Additionally, when applied in this manner, the flexible restrictor preferably has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.
10
15

In another preferred embodiment, the reagent is applied to the test pad in an discrete amount to the reaction area of the pad. When applied in this manner,
20 the nozzle has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches. Preferably, in this embodiment, the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.
25

Preferably, the oxidase enzyme employed in the test strip is selected from the group consisting of glucose oxidase, cholesterol oxidase, uricase, alcohol oxidase, aldehyde oxidase and glycerophosphate oxidase. More preferably, the oxidase enzyme is glucose oxidase.

30 The indicator system employed in this invention is preferably selected from the group consisting of (a) 3-methyl-2-benzothiazolinone hydrazone

-5-

hydrochloride and 3-dimethylaminobenzoic acid; (b) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 3,5-dichloro-2-hydroxybenzenesulfonic acid; (c) 4-aminoantipyrene and 5-oxo-1-(p-sulfophenyl)-2-pyrazoline-3-carboxylic acid; (d) 4-aminoantipyrene and N-(m-tolyl)-diethanolamine; (e) 4-aminoantipyrene and 4-methoxynaphthol; (f) 2,2'-azino-di-(3-ethylbenzthiazoline)sulfonic acid; (g) pyrogallol red; (h) bromopyrogallol red; (i) acid green 25; (j) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 8-anilino-1-naphthalenesulfonate; (k) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and N-(3-sulfopropyl)aniline; (l) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 3-dimethylaminobenzoic acid; (m) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 8-anilino-1-naphthalenesulfonate; and (n) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and N-(3-sulfopropyl)aniline.

15

Using the methods of this invention, the reagent can be applied to multiple tracks of test pad thereby increasing the throughput of the system.

Alternatively, the methods of this invention can be employed to apply or lay down different concentrations of reagent on isolated test pads.

20

In one preferred embodiment, the fluid delivery system comprises a plurality of nozzles and flexible restrictors. Preferably, the multiple nozzle are joined together to form a slotted-head applicator. If desired, each of the plurality of nozzles and flexible restrictors can apply a different concentration of reagent to the test pad thereby creating a gradient effect between each application of reagent. Alternatively, each nozzle and flexible restrictor can be used to apply a different reagent to the test pad.

25 In another of its aspects, the present invention provides an apparatus for applying a reagent to a test device comprising a substrate and a test pad, said apparatus comprising:

-6-

- (a) a fluid delivery system comprising a nozzle and a flexible restrictor for delivery of the reagent to the test pad;
- (b) a support positioned under the fluid delivery system for supporting the test device; and
- 5 (c) means for moving the test device under the fluid delivery system.

In a preferred embodiment, the fluid delivery system of the apparatus further comprises a pressure delivery system. The pressure delivery system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

10 In another preferred embodiment, the fluid delivery system of the apparatus further comprises a positive displacement system. The positive displacement system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

15 In still another preferred embodiment, a brush (such as a felt pad) is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad.

20 In a preferred embodiment, the nozzle employed in the apparatus has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches. In this embodiment, the flexible restrictor preferably has an internal diameter ranging from about 0.002 to about 25 0.200 inches and a length of about 0.5 to about 12 feet. This embodiment of the apparatus is particularly preferred for applying the reagent in a continuous manner.

30 In another preferred embodiment, the nozzle employed in the apparatus has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches. In this embodiment, the flexible

-7-

restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet. This embodiment of the apparatus is particularly preferred for applying discrete amounts of the reagent to the test pad.

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In a preferred embodiment of the apparatus, the means for moving the test device is a conveyor.

10 In another preferred embodiment, the fluid delivery system comprises a plurality of nozzles and flexible restrictors. Preferably, the each of the plurality of nozzles and flexible restrictors is employed to apply a different concentration of the reagent thereby creating a gradient effect between each application of reagent.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a view of a continuous multi-nozzle coating system using a long flexible restrictor and a pressure delivery system.

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Figure 2 is a view of a continuous multi-nozzle coating system using a long flexible restrictor and a positive displacement delivery system.

Figure 3 is a view of a discrete multi-nozzle coating system using a long flexible restrictor and a pressure delivery system.

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Figure 4 is a view of a discrete multi-nozzle coating system using a long flexible restrictor and a positive displacement delivery system.

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Figure 5 is a view of a nozzle system with brushes to dampen pump pulsation.

-8-

Figure 6 is a view of a slotted-head multiple nozzle.

Figure 7 is a view of a slotted-head multiple nozzle coating system using a long flexible restrictors and a pressure delivery system.

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Figure 8 is a view of a slotted-head multiple nozzle with a brush (felt pad) attached.

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DETAIL DESCRIPTION OF THE INVENTION

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Test devices made using the methods and fluid delivery systems of the present invention to imbibe the reagent into the test pad use complete or partial prefabricated test devices. The test devices move either on a conveyor suitable for moving the test devices or as a continuous web. The amount of fluid required and the coverage is calculated so that the appropriate volume of reagent is dispensed on the device test pad.

20

For continuous deposition, the fluid delivery system dispenses a continuous stream of reagent. The length of the restrictor, the size of the nozzle, and the system pressure are selected using an iterative process to determine the amount of reagent delivered. The amount of fluid delivered is directly linked to the internal diameter (id) of the restrictor and nozzle and the length of each. For volumes in the range of less than one milliliter per minute, the nozzle id preferably ranges from about 0.005 to about 0.150 inches (about 0.0127 to about 0.381 cm) and has a length of about 0.2 to about 2.0 inches (about 0.51 to about 5.1 cm). To minimize any pulsation in the system, the restrictors preferably have an id of from 0.002 to 0.200 inches (about 0.011 to about 0.51 cm) and a length of about 0.5 to 12 feet (about 0.152 to about 3.66 m) depending on the temperature of the surrounding environment. Preferably, the restrictors are made from a flexible tubing, such as nylon or tygon. This creates a slight accumulation capacity in the system to damp out any pulsation. The nozzle size

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-9-

for this example would have an id of 0.015 inches and a length of 6 inches. The composition of the nozzle is preferably PVC plastic, stainless steel or glass.

For discrete deposition, the invention generally dispenses a pre-determined amount of reagent, typically in the form of a drop. The length of the restrictor, the size of the nozzle and system pressure are selected using a similar iterative process as described above. However, to determine nozzle length and size, the amount to be delivered to an application site must be determined and the nozzles selected with a suitable end which can support formation of an adequate drop. The amount of fluid delivered is directly linked to the nozzle tip dimensions and shape, and to the internal diameter (id) of the restrictor and nozzle and the length of each. For volumes in the range of less than one milliliter per minute, the nozzle id is preferably less than or equal to 0.032 inches (0.0813 cm) and the length is preferably about 0.2 to about 2.0 inches (about 0.51 to about 5.1 cm). The restrictors preferably have an id of from 0.002 to about 0.200 inches (about 0.011 to about 0.51 cm) and a length of about 0.5 to about 12 feet (about 0.152 to about 3.66 m) depending on the temperature of the surrounding environment. To minimize any pulsation in the system, the restrictors are preferably made from a flexible tube such as nylon or tygon. This creates a slight accumulation capacity in the system to damp out any pulsation. The nozzle size for this example would have an id of 0.015 inches and a length of 6 inches. The composition of the nozzle is preferably PVC plastic, stainless steel or glass.

The opening of the nozzles employed in this invention may have any art-recognized shape, including round, oval or slit nozzles. The nozzle shape will typically be chosen based on the amount and the surface area of reagent desired on the test pad.

-10-

The fluid delivery system in either case typically further comprises a positive displacement system or pressure system. Examples of positive displacement systems include gravity feed systems and the like. Pressure systems include syringes, continuous flow pumps and the like. Pressure delivery systems for discrete reagent application require very fine pressure control and sharp on/off switching capabilities. A system such as those built by EFD corporation of Providence, RI (Model 1000DV) is suitable for use in this invention. Syringe pumps made by ISCO pump or Harvard Apparatus can also accommodate the deliver requirements for low volume discrete deliver applications.

Pumps create pulsations due to sticking of the seals or peristaltic action. If the flexible restrictors and nozzles are not sufficient to dampen these pulsation, a brush is preferably used on the underside to provide a path for the reagent to the membrane. The term brush refers to any object which serves to spread the reagent on the surface of the pad, including brushes with bristles and other spreading objects such as felt pads and the like.

In one of its embodiments, the present invention employs a plurality of nozzles and flexible restrictors. In this embodiment, the nozzles can be joined together to form a slotted-head. The various nozzles and flexible restrictors allow different concentrations of the reagent to be applied to the test pad. This creates a concentration gradient across the test pad. Alternatively, different reagents can be applied through each of the nozzles

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The reagent system used in this invention must be capable of detecting the presence of the analyte. In general, the analyte reacts with a specific oxidase or peroxidase enzyme and produces hydrogen peroxide. This strongly oxidative substance reacts with the indicator(s) present to produce a colored end product. Preferred oxidase enzymes for use in this invention include, but are not limited to, the following: glucose oxidase, cholesterol oxidase, uricase, alcohol oxidase,

-11-

aldehyde oxidase or glycerophosphate oxidase. Other oxidase or peroxidase enzymes will be readily evident to one who is skilled in the art.

The indicator chemistries which provide acceptable color generation when applied to the test pad may be chosen from 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) combined with 3-dimethylaminobenzoic acid (DMAB), MBTH combined with 3,5-dichloro-2-hydroxybenzene-sulfonic acid (DCHBS); 4-aminoantipyrene (4-AAP) and 5-oxo-1-(p-sulfophenyl)-2-pyrazoline-3-carboxylic acid (OPSP); 4-AAP and N-(m-tolyl)-diethanolamine (NDA); 2,2'-azino-di-(3-ethylbenzthiazoline)sulfonic acid (ABTS); 4-AAP and 4-methoxynaphthol; pyrogallol red (PGR); bromopyrogallol red (BPR); acid green 25 (AG); MBTH and 8-anilino-1-naphthalenesulfonate (ANS); or N-(3-sulfopropyl)aniline and MBTH; or other known and conventional dye system for different analytes. U.S. Patent No. 5,306,623 to Kiser et. al. discloses effective concentrations of a number of useful dye systems. Many other indicator reagent systems are known in the art and any of these may be used in this invention.

A preferred dye system is based on the sulfonated form of MBTH, 3-methyl-6-(M sulfonate)-benzothiazolinone-(2)-hydrazone (MBTH-S) where M is sodium, potassium, ammonium or other equivalent ion, but is preferably sodium. Sulfonation of MBTH to form MBTH-S is disclosed in U.S. Patent 4,101,381 to Klose. MBTH-S formed as a dye couple with DMAB, ANS or N-(3-sulfopropyl)aniline provides preferred indicator systems having stable color end points in a short period of time.

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The particular reagent system employed in this invention will determine, in part, the id and length of the nozzle and the restrictor employed. Typically, a smaller id and/or a longer length for the nozzle and/or the restrictor will be used when the reagent has a lower viscosity. Alternatively, the viscosity of the 30 reagent can be modified or optimized for a particular delivery system by the addition to the reagent of well-known viscosity modifying agents and/or by

-12-

controlling the temperature of the reagent. In the latter case, the reagent can be warmed or cooled by heating or cooling the restrictors and/or the reagent reservoirs. For example, the restrictors and reagents reservoirs can be cooled to the desired temperature by immersing the restrictors and reservoirs in an ice bath
5 or by surrounding them with a refrigeration system. Similiarly, heating may be accomplished using a warm water bath or an oven. Depending on the reagent, cooling of the restrictors and reagent reserviors also has the additional benefit of stabilizing the reagent system thereby preventing or reducing the decomposition of the reagent. Accordingly, the length of time the reagent is useable may be
10 significantly increased.

A further description of this invention may be obtained from the drawings.

15 Figure 1 is a view of a continuous multi-nozzle coating system using a long flexible restrictor 1 and a pressure pot delivery system 8 and nozzle 3. The reagent is dispensed from the nozzle and test pad 5 is impregnated.

20 Figure 2 is a view of a continuous multi-nozzle coating system using a long flexible restrictor 1 and a positive displacement delivery system 4 and nozzles 3. The reagent is dispensed from the nozzle and test pad 5 is impregnated.

25 Figure 3 is a view of a discrete multi-nozzle coating system using a long flexible restrictor 1 and a pressure delivery system 8 and nozzles 3. The reagent is dispensed from the nozzle and test pad 5 is impregnated.

Figure 4 is a view of a discrete multi-nozzle coating system using a long flexible restrictor 1 and a positive displacement delivery system 4 and nozzles 3.
30 The reagent is dispensed from the nozzle and test pad 5 is impregnated.

-13-

Figure 5 is a view of a nozzle system with nozzle 3 and brushes 7 to dampen pump pulsation and provide flow control. If the flexible restrictors and nozzles are not sufficient to dampen these pulsation, a brush is used on the underside to provide a path for the reagent to the membrane.

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Figure 6 is a view of a multiple slotted-head nozzle 8 having multiple openings 9 for delivery of multiple reagents or different concentrations of reagents to a test pad.

10

Figure 7 is a view of a multiple slotted-head nozzle coating system using long flexible restrictors 1 and a pressure delivery system 4 and a multiple slotted-head nozzle 8. The reagent is dispensed from the nozzle to the test pad.

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Figure 8 is a view of a multiple slotted-head nozzle coating system using long flexible restrictors 1 and a pressure delivery system 4 and a multiple slotted-head nozzle 8 having a felt pad 10 attached. The reagent is dispensed from the nozzle through the felt pad to the test pad 5.

-14-

WHAT IS CLAIMED IS:

1. A method for applying a reagent to a test device comprising:
 - (a) providing a test device comprising a substrate and a test pad attached to the substrate;
 - (b) providing a fluid delivery system comprising a nozzle and a flexible restrictor attached to the nozzle for delivery of a reagent from the nozzle to the test pad;
 - (c) applying a reagent comprising an indicator system and an oxidase enzyme or a peroxidase enzyme in a predetermined amount and at a predetermined pressure through the nozzle and the flexible restrictor to the test pad.
- 10 2. The method of Claim 1 wherein the fluid delivery system further comprises a pressure delivery system.
- 15 3. The method of Claim 1 wherein the fluid delivery system further comprises a positive displacement system.
- 20 4. The method of Claim 1 wherein a brush is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad.
- 25 5. The method of Claim 1 wherein the reagent is applied continuously to the test pad.
- 30 6. The method of Claim 5 wherein the nozzle has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

-15-

7. The method of Claim 1 wherein the reagent is applied in a discrete amount to the test pad.

8. The method of Claim 7 wherein the nozzle has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

9. The method of Claim 1 wherein the oxidase enzyme is selected from the group consisting of glucose oxidase, cholesterol oxidase, uricase, alcohol oxidase, aldehyde oxidase and glycerophosphate oxidase.

10. The method of Claim 1 wherein the indicator system is selected from the group consisting of (a) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 3-dimethylaminobenzoic acid; (b) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 3,5-dichloro-2-hydroxybenzenesulfonic acid; (c) 4-aminoantipyrene and 5-oxo-1-(p-sulfophenyl)-2-pyrazoline-3-carboxylic acid; (d) 4-aminoantipyrene and N-(m-tolyl)-diethanolamine; (e) 4-aminoantipyrene and 4-methoxynaphthol; (f) 2,2'-azino-di(3-ethylbenzthiazoline)sulfonic acid; (g) pyrogallol red; (h) bromopyrogallol red; (i) acid green 25; (j) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 8-anilino-1-naphthalenesulfonate; (k) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and N-(3-sulfopropyl)aniline; (l) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 3-dimethylaminobenzoic acid; (m) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 8-anilino-1-naphthalenesulfonate; and (n) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and N-(3-sulfopropyl)aniline.

11. The method of Claim 1 wherein the fluid delivery system comprises a plurality of nozzles and flexible restrictors.

-16-

12. The method of Claim 11 wherein each of the plurality of nozzles and flexible restrictors applies a different concentration of reagent to the test pad.

13. An apparatus for applying a reagent to a test device comprising a substrate and a test pad, said apparatus comprising:

- (a) a fluid delivery system comprising a nozzle and a flexible restrictor for delivery of the reagent to the test pad;
- (b) a support positioned under the fluid delivery system for supporting the test device; and
- 10 (c) means for moving the test device under the fluid delivery system.

14. The apparatus of Claim 13 wherein the fluid delivery system further comprises a pressure delivery system.

15 15. The apparatus of Claim 13 wherein the fluid delivery system further comprises a positive displacement system.

16. The apparatus of Claim 13 wherein a brush is attached to the underside of the nozzle and the reagent is applied through the nozzle and then 20 through the brush to the test pad.

17. The apparatus of Claim 13 wherein the nozzle has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal 25 diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

18. The apparatus of Claim 13 wherein the nozzle has an internal diameter which is less than or equal to 0.032 inches and a length ranging from 30 about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter

-17-

ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

19. The apparatus of Claim 13 wherein the means for moving the test
5 device is a conveyor.

20. The apparatus of Claim 13 wherein the fluid delivery system
comprises a plurality of nozzles and flexible restrictors.

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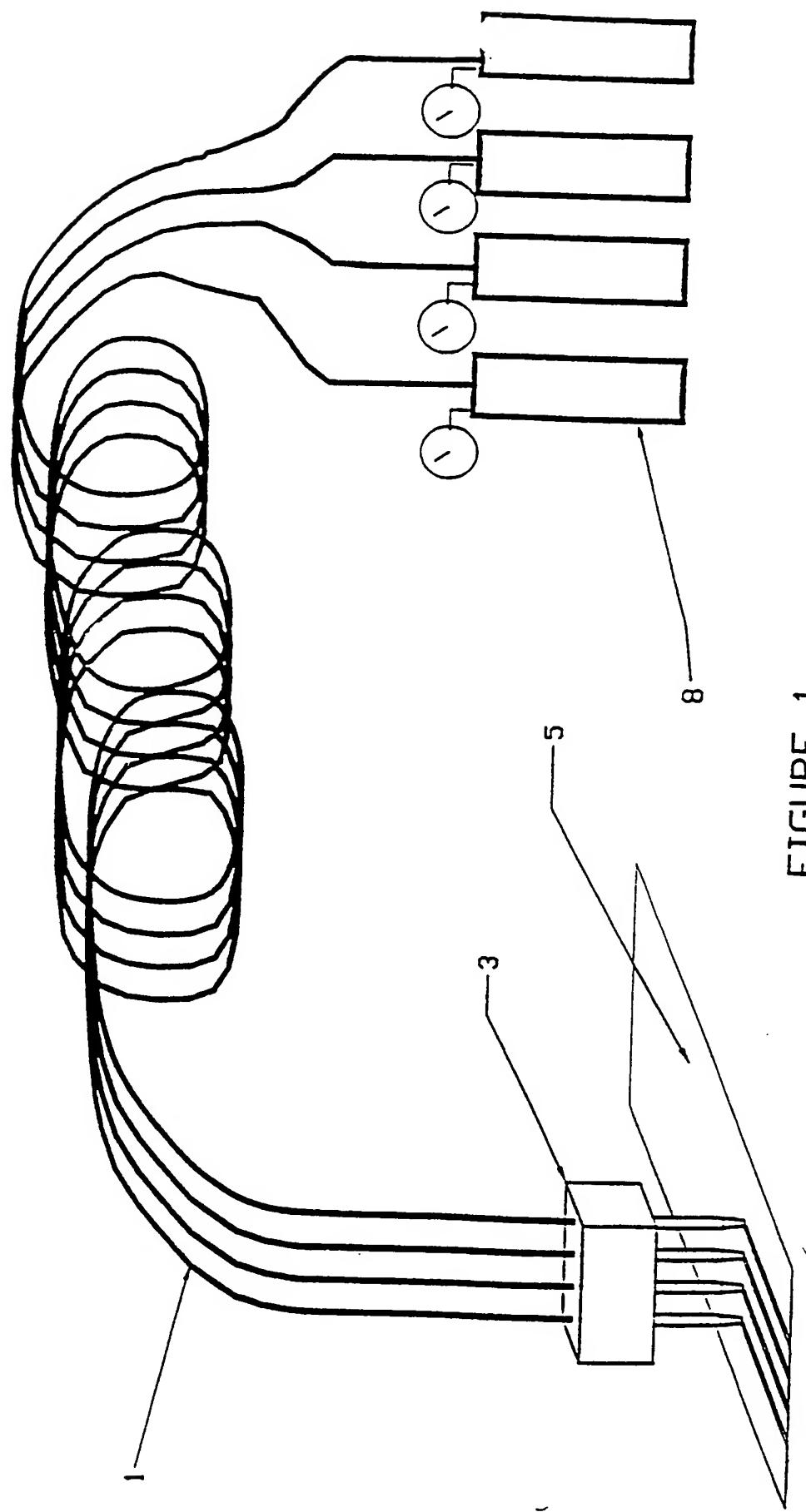


FIGURE 1

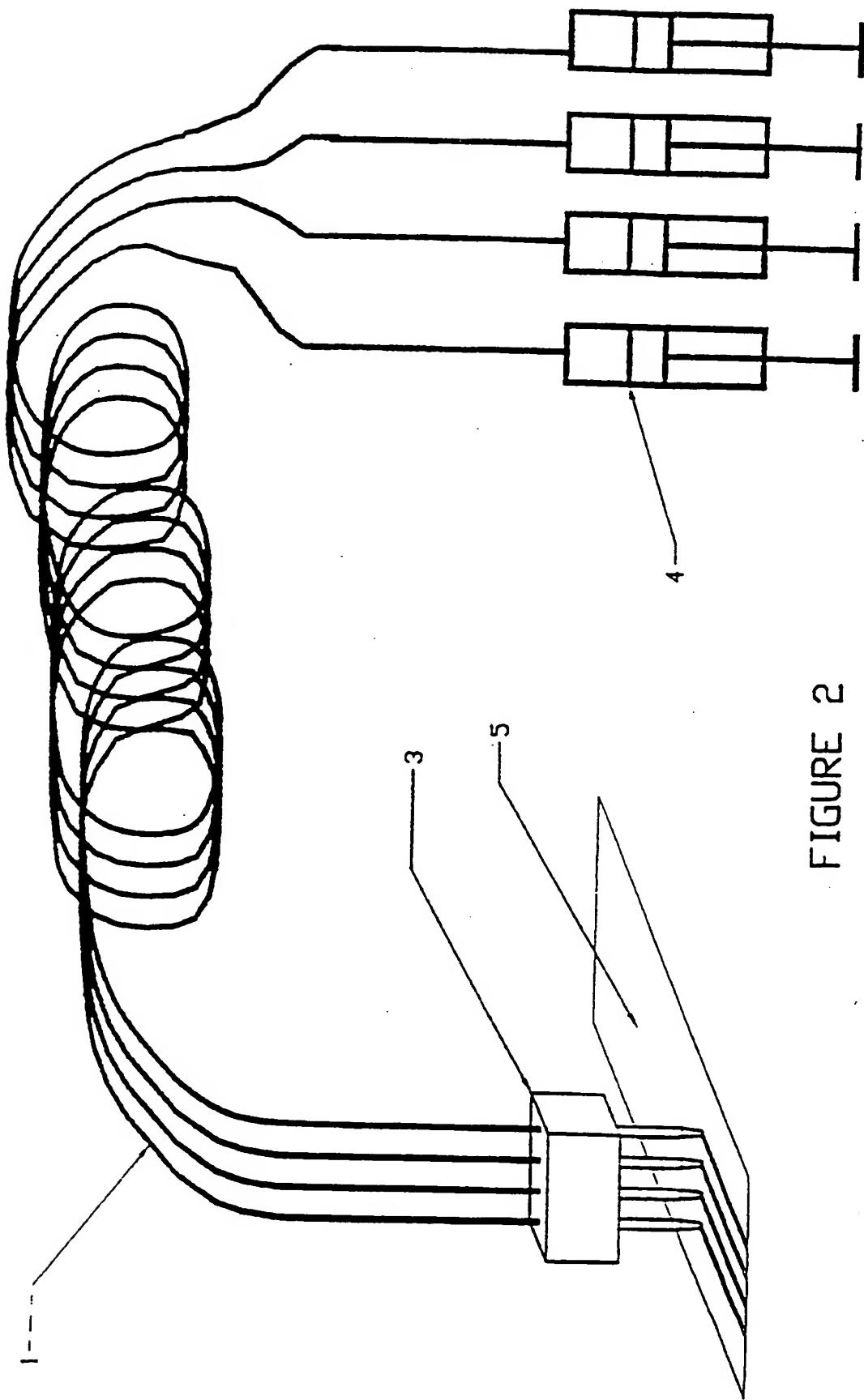


FIGURE 2

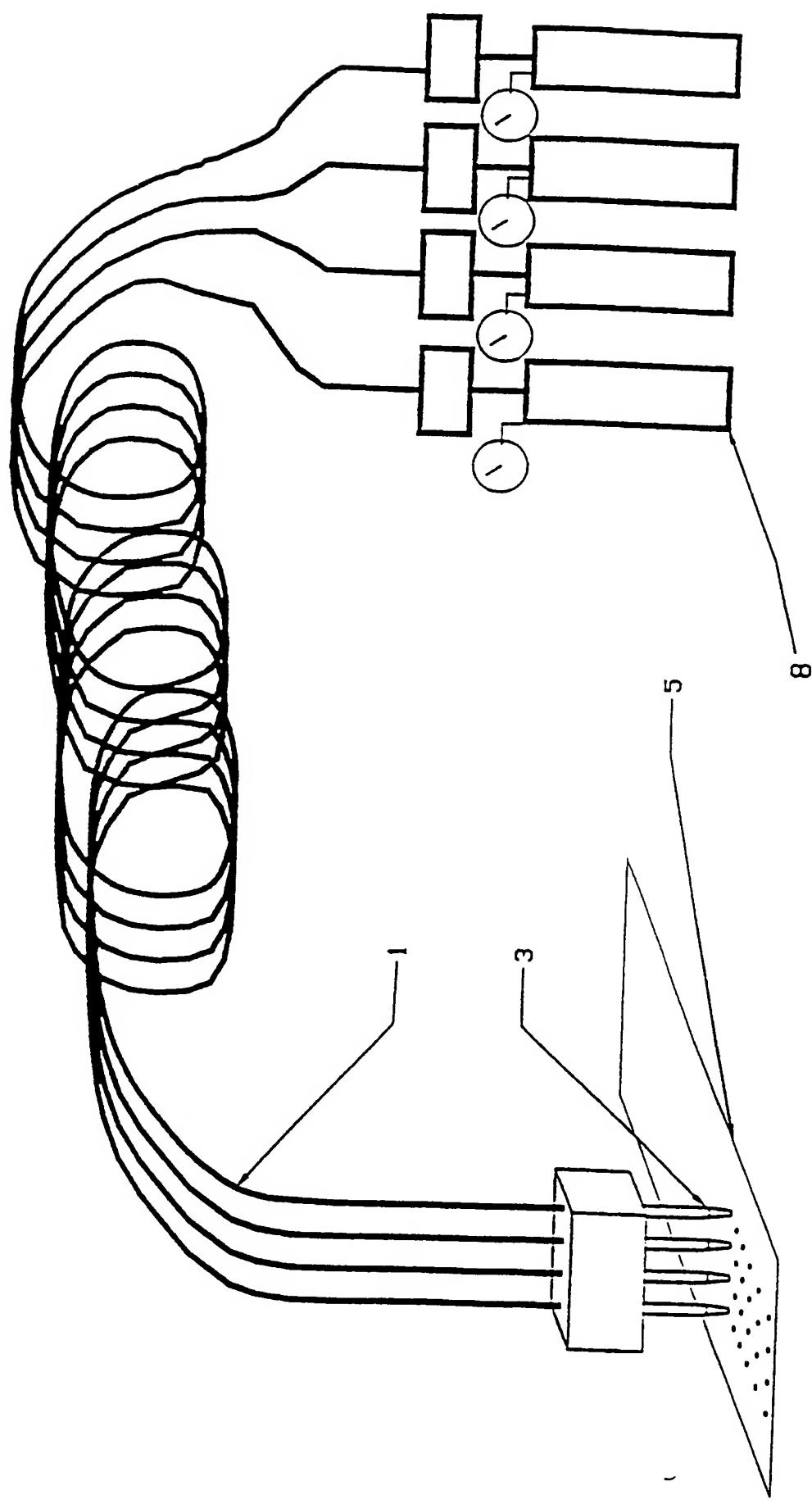


FIGURE 3

4/8

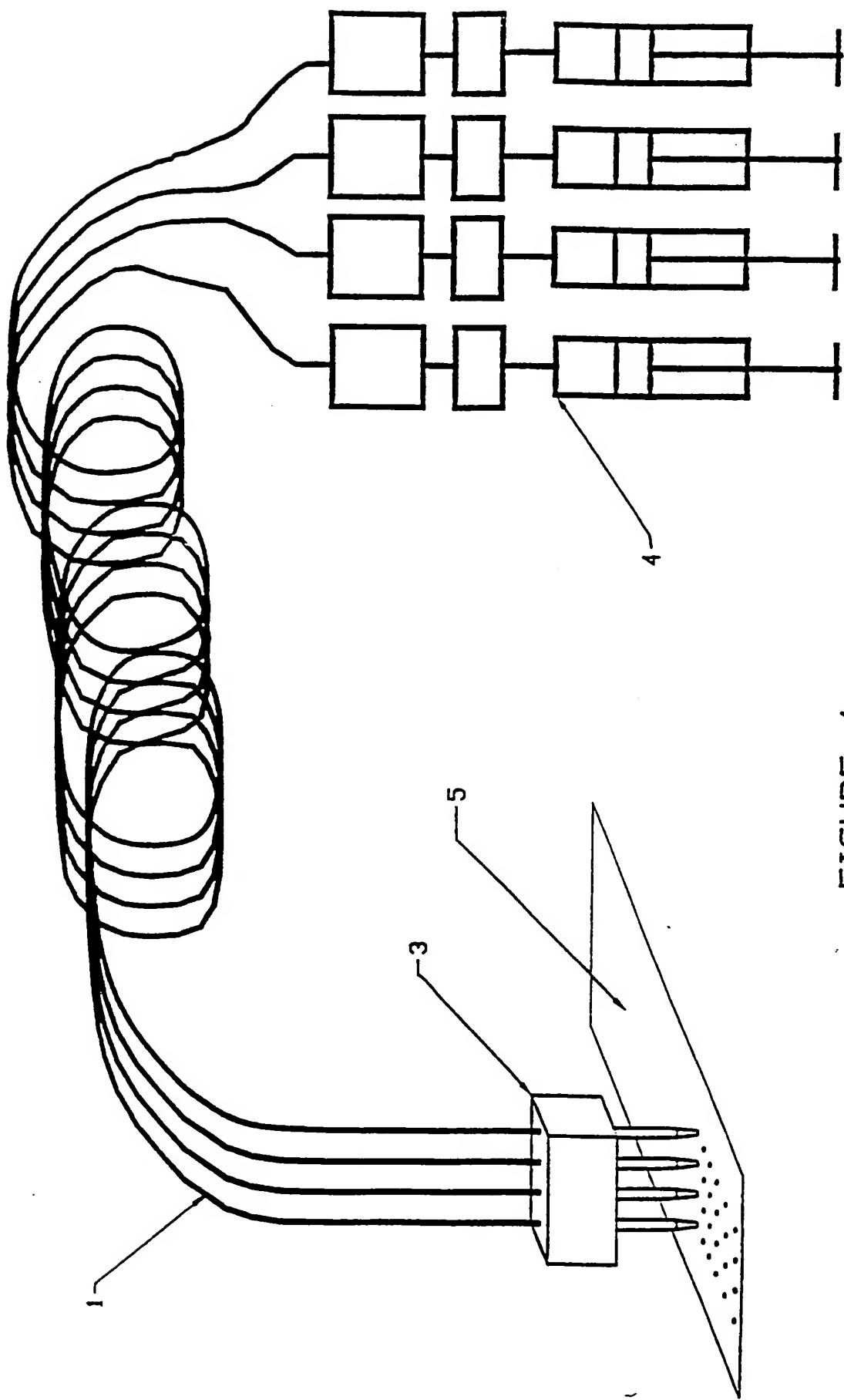
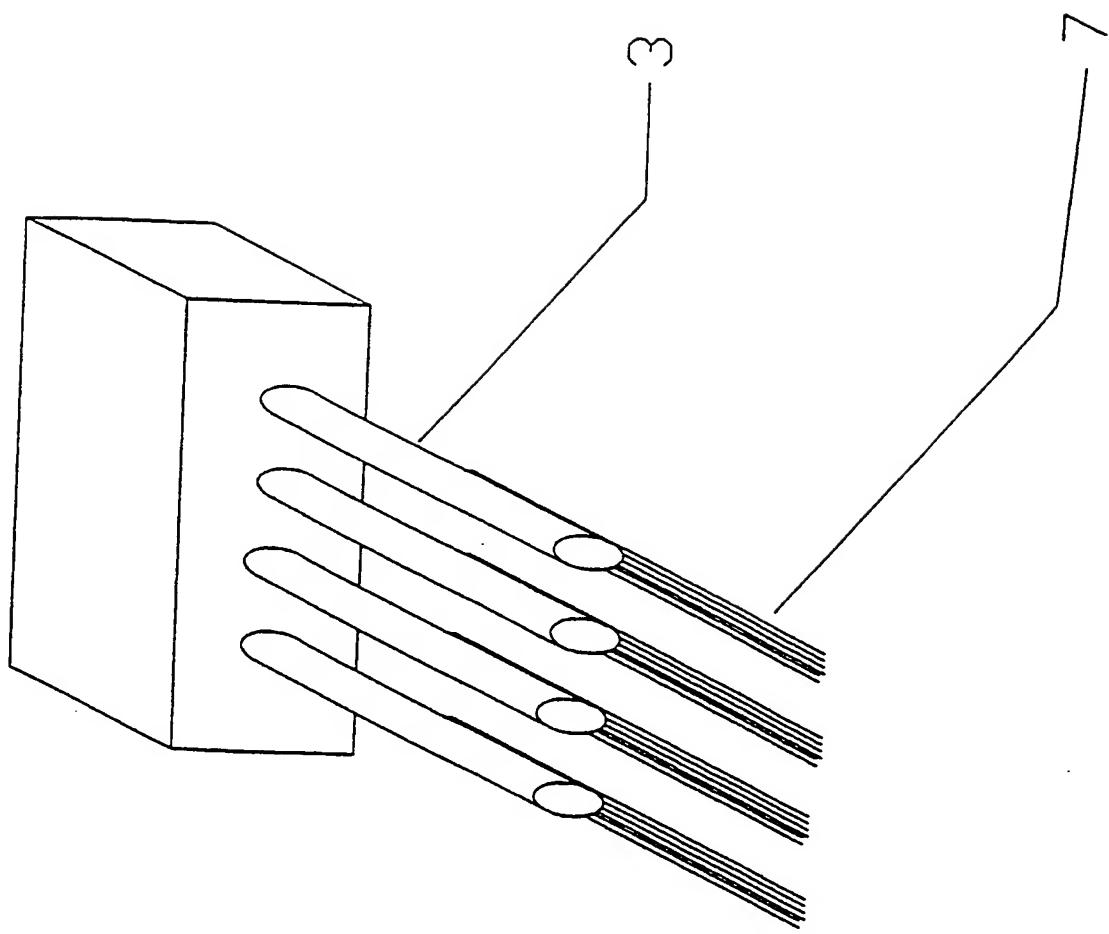


FIGURE 4

5/8

Figure 5



6/8

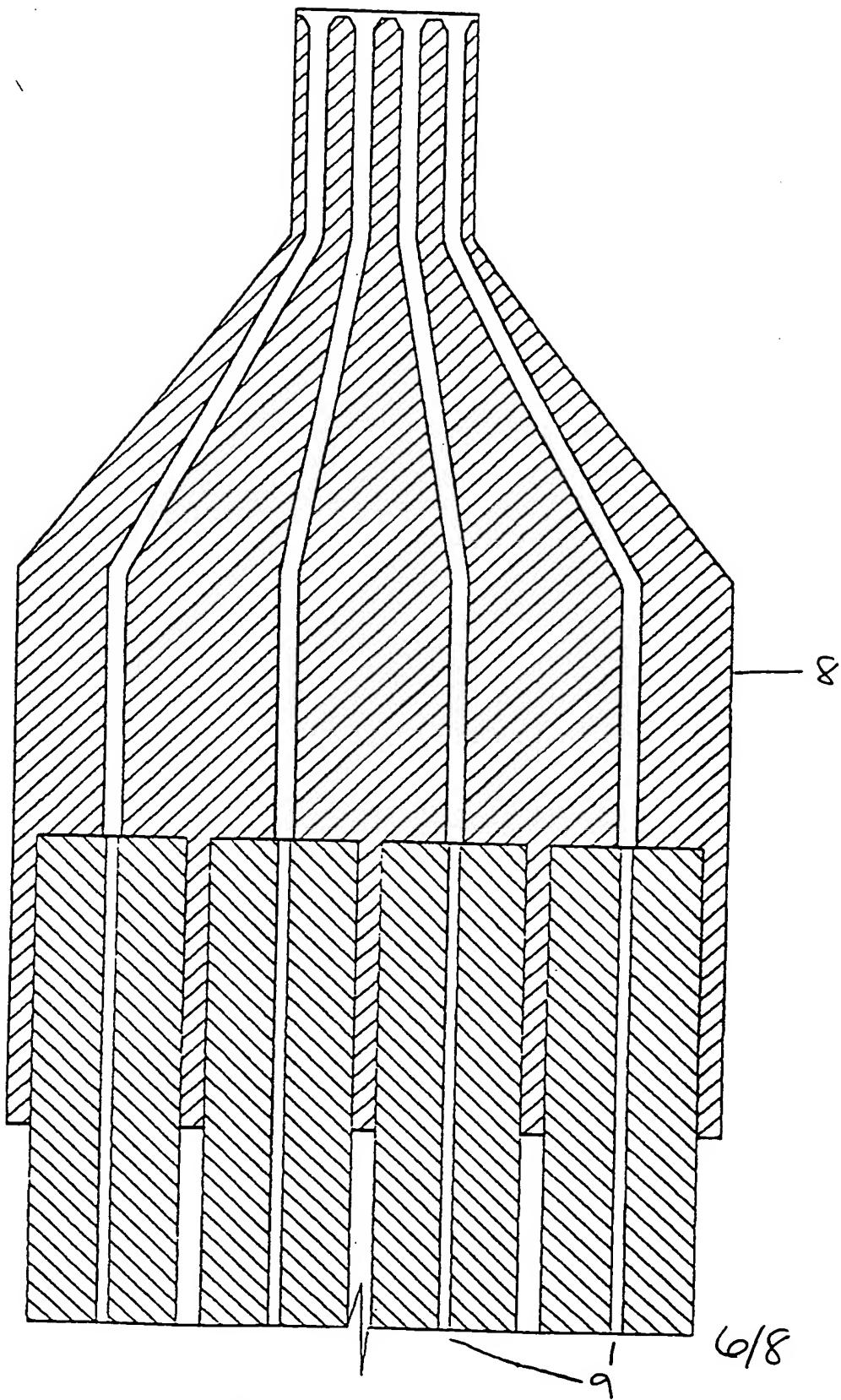


FIGURE 6

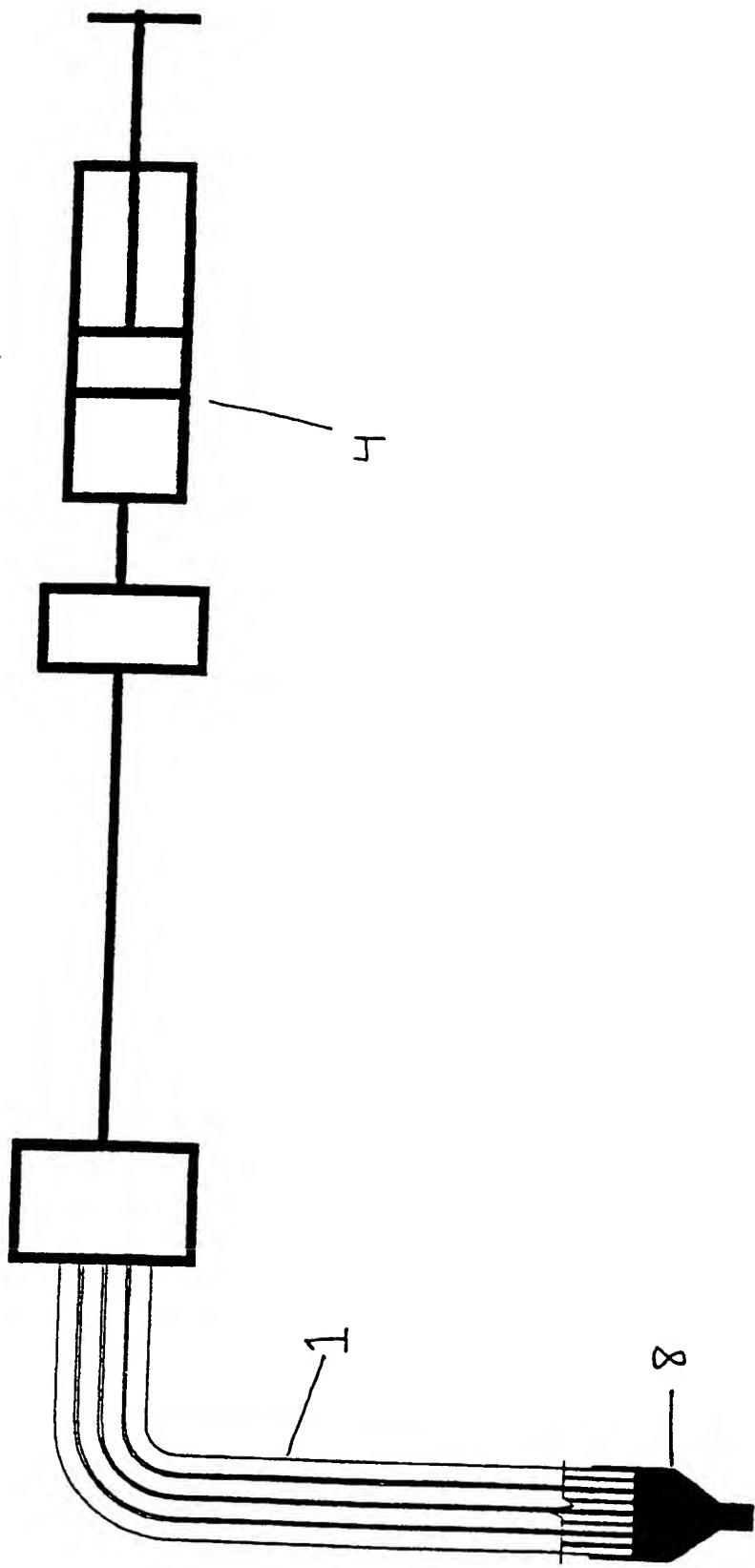
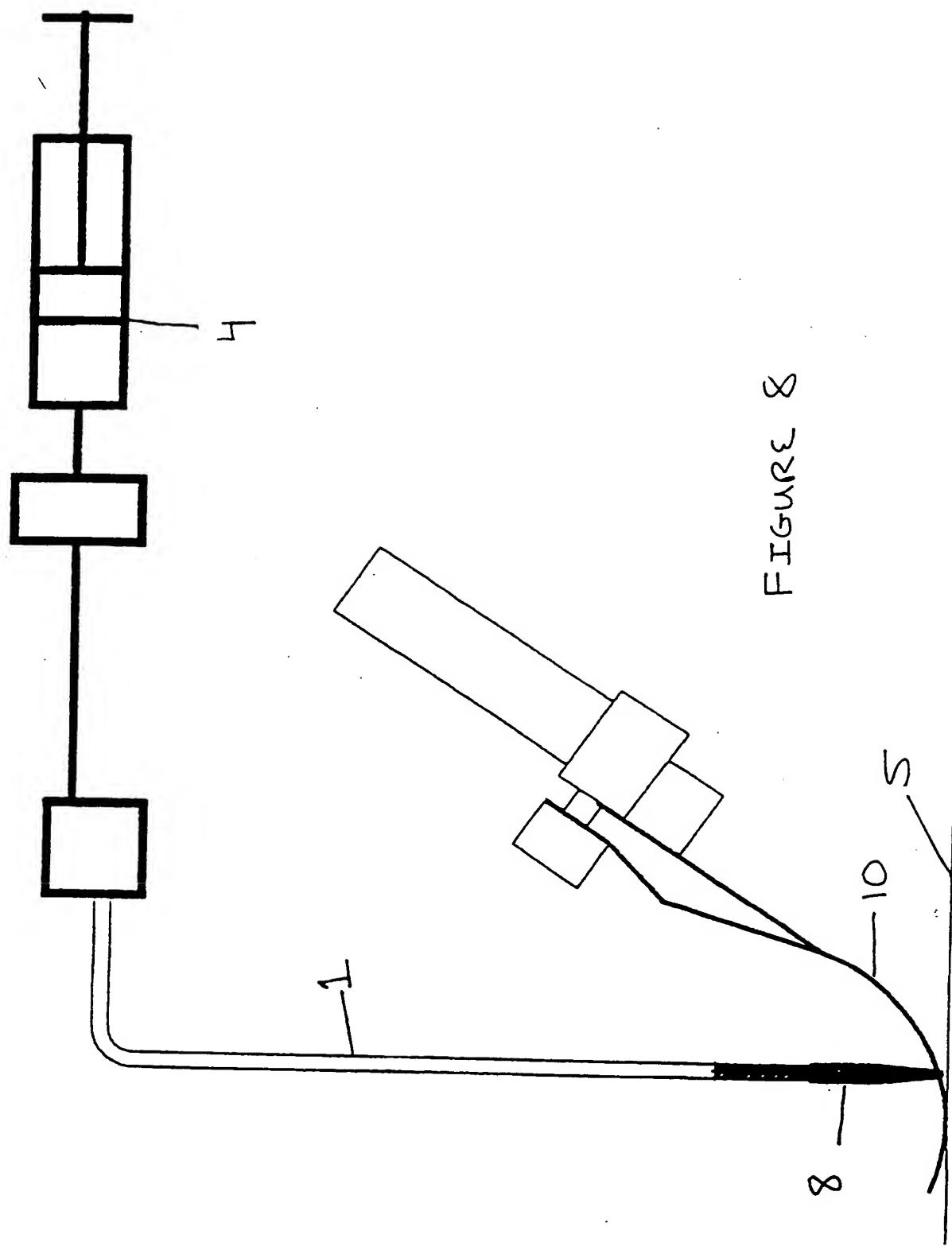


FIGURE 7

8/8



INTERNATIONAL SEARCH REPORT

ional Application No

PCT/US 98/00477

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 G01N33/52 C1201/26 //B05C5/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 G01N C12Q B05C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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20 April 1998

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Koch, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/00477

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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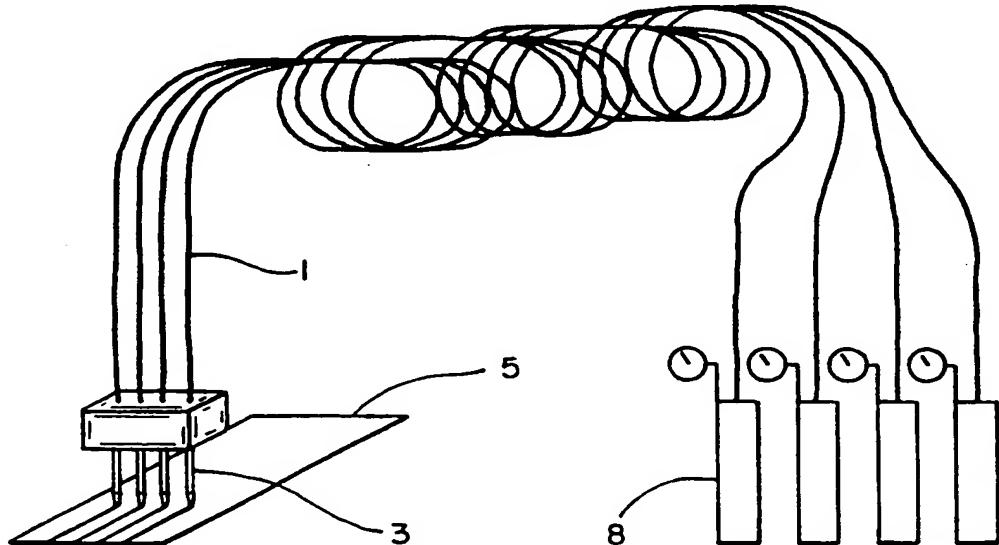
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : G01N 33/52, C12Q 1/26 // B05C 5/02		A1	(11) International Publication Number: WO 98/30904 (43) International Publication Date: 16 July 1998 (16.07.98)
<p>(21) International Application Number: PCT/US98/00477</p> <p>(22) International Filing Date: 8 January 1998 (08.01.98)</p> <p>(30) Priority Data: 60/034,668 9 January 1997 (09.01.97) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/034,668 (CON) Filed on 9 January 1997 (09.01.97)</p> <p>(71) Applicant (<i>for all designated States except US</i>): MERCURY DIAGNOSTICS, INC. [US/US]; Suite D, 1137 San Antonio Road, Palo Alto, CA 94303 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): DOUGLAS, Joel, S. [US/US]; 2048 Calabazas Boulevard, Santa Clara, CA 95051 (US). GLEISNER, John, M. [US/US]; 20504 52nd Avenue West, Lynnwood, WA 98036 (US).</p> <p>(74) Agents: DILLAHUNTY, T., Gene et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	

(54) Title: METHOD FOR APPLYING A REAGENT TO AN ANALYTICAL TEST DEVICE



(57) Abstract

This invention provides methods and apparatus for applying a reagent to an analytical test device. The methods and apparatus employ a nozzle and a flexible restrictor to accurate control the amount of reagent applied to the test device. The analytical test devices prepared by the methods of this invention are used to determine the presence or the quantity of an analyte in a liquid sample, such as whole blood.

*(Referred to in PCT Gazette No. 45/1998, Section II)

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METHOD FOR APPLYING A REAGENT TO AN ANALYTICAL TEST DEVICE

5

BACKGROUND OF THE INVENTION

Field of Invention

This invention relates to improved methods for applying a reagent to an analytical test device. The test devices prepared by the methods of this invention are typically used to determine the presence and/or the quantity of an analyte in a liquid test sample, such as whole blood. This invention also provides apparatus for applying the reagent to the analytical test device.

State of the Art

Analytical test devices containing a reagent are commonly used to determine the presence or the quantity of a particular analyte in liquid samples, such as whole blood. For example, diabetics typically use such test devices to monitor the level of glucose in their blood. The reagent on the test device typically indicates the presence or the quantity of the analyte in the liquid sample using either spectrophotographic, color match or electrochemical technology. Such test devices generally comprise a substrate, such as a non-porous handle, and an absorbent test pad attached to the handle. The reagent is typically applied to the test pad either before or after assembly and then dried to create a "dry" chemical test device.

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-2-

Numerous methods of applying reagents and coatings to analytical test devices have been described in the literature. These methods include dip coating, roll coating, ink jet application, screen printing, brushing, painting and the like.

5 For example, Bertek, Inc. literature entitled "The Technology of Coating and Laminating" (1986) describes various coating technologies and techniques, including roll coating, knife over roll and slot coating methods. These methods typically apply the reagents either across the whole web of the test device or in a continuous manner.

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Similarly, U.S. Patent 5,547,702 to Gleisner, describes a method of applying a reagent mixture down a reagent test pad in a continuous manner.

15 Many other patents describe imbibing processes such as dip coating processes. For example, U.S. Patent 4,935,346 to Phillips et al., describes a process in which a membrane is dip coated and then dried.

20 When the test devices prepared by such methods are used to determine the quantity of an analyte in a liquid sample, it is particularly important that the amount of reagent deposited on the test device be accurately controlled so that reproducible test results are achieved. Additionally, the reagents employed in the test devices are often expensive and need to be conserved. Therefore, it is particularly important that the reagent be applied to the test device only where it is needed. Accordingly, it would highly desirable to develop novel methods and 25 apparatus for applying the reagent to the test device such the reagent is deposited on the test device in an accurate and controlled manner.

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SUMMARY OF THE INVENTION

The present invention provides improved methods and apparatus for applying a reagent to an analytical test device. The methods and apparatus of this invention employ flexible restrictors to accurately control the amount of reagent applied to the test device. Such restrictors allow the reagent to be applied to the test device in a predetermined amount thereby providing reproducible test results. Applying the reagent with such restrictors also allows the reagent to be applied only where it is needed thus conserving expensive reagents.

10

Accordingly, in one of its method aspects, the present invention provides a method for applying a reagent to a test device comprising:

- (a) providing a test device comprising a substrate and a test pad attached to the substrate;
- 15 (b) providing a fluid delivery system comprising a nozzle and a flexible restrictor attached to the nozzle for delivery of a reagent from the nozzle to the test pad;
- (c) applying a reagent comprising an indicator system and an oxidase enzyme or a peroxidase enzyme in a predetermined amount and at a 20 predetermined pressure through the nozzle and the flexible restrictor to the test pad.

In a preferred embodiment of this invention, the fluid delivery system further comprises a pressure delivery system. The pressure delivery system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

In another preferred embodiment, the fluid delivery system further comprises a positive displacement system. The positive displacement system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

-4-

In still another preferred embodiment, a brush is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad. In this embodiment, the brush applies or paints the reagent onto the test pad. In addition to applying the reagent more evenly on the test
5 pad, the brushes also provide additional damping of any pulsation from the pumping system.

The reagent can be applied to the test pad continuously or in a discrete amount. Accordingly, in a preferred embodiment of this invention, the reagent is
10 applied to the test pad in a metered amount continuously down the length of the pad. When the reagent is applied continuously to the test pad, the nozzle preferably has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches. Additionally, when applied in this manner, the flexible restrictor preferably has an internal
15 diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

In another preferred embodiment, the reagent is applied to the test pad in an discrete amount to the reaction area of the pad. When applied in this manner,
20 the nozzle has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches. Preferably, in this embodiment, the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

25 Preferably, the oxidase enzyme employed in the test strip is selected from the group consisting of glucose oxidase, cholesterol oxidase, uricase, alcohol oxidase, aldehyde oxidase and glycerophosphate oxidase. More preferably, the oxidase enzyme is glucose oxidase.

30 The indicator system employed in this invention is preferably selected from the group consisting of (a) 3-methyl-2-benzothiazolinone hydrazone

-5-

hydrochloride and 3-dimethylaminobenzoic acid; (b) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 3,5-dichloro-2-hydroxybenzenesulfonic acid; (c) 4-aminoantipyrine and 5-oxo-1-(p-sulfophenyl)-2-pyrazoline-3-carboxylic acid; (d) 4-aminoantipyrine and N-(m-tolyl)-diethanolamine; (e) 4-aminoantipyrine and 4-methoxynaphthol; (f) 2,2'-azino-di-(3-ethylbenzthiazoline)sulfonic acid; (g) pyrogallol red; (h) bromopyrogallol red; (i) acid green 25; (j) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 8-anilino-1-naphthalenesulfonate; (k) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and N-(3-sulfopropyl)aniline; (l) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 3-dimethylaminobenzoic acid; (m) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 8-anilino-1-naphthalenesulfonate; and (n) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and N-(3-sulfopropyl)aniline.

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Using the methods of this invention, the reagent can be applied to multiple tracks of test pad thereby increasing the throughput of the system. Alternatively, the methods of this invention can be employed to apply or lay down different concentrations of reagent on isolated test pads.

20

In one preferred embodiment, the fluid delivery system comprises a plurality of nozzles and flexible restrictors. Preferably, the multiple nozzle are joined together to form a slotted-head applicator. If desired, each of the plurality of nozzles and flexible restrictors can apply a different concentration of reagent to the test pad thereby creating a gradient effect between each application of reagent. Alternatively, each nozzle and flexible restrictor can be used to apply a different reagent to the test pad.

30 In another of its aspects, the present invention provides an apparatus for applying a reagent to a test device comprising a substrate and a test pad, said apparatus comprising:

-6-

- (a) a fluid delivery system comprising a nozzle and a flexible restrictor for delivery of the reagent to the test pad;
- (b) a support positioned under the fluid delivery system for supporting the test device; and
- 5 (c) means for moving the test device under the fluid delivery system.

In a preferred embodiment, the fluid delivery system of the apparatus further comprises a pressure delivery system. The pressure delivery system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

10 In another preferred embodiment, the fluid delivery system of the apparatus further comprises a positive displacement system. The positive displacement system feeds the reagent into the flexible restrictor in a controlled manner for application to the test pad through the nozzle.

15 In still another preferred embodiment, a brush (such as a felt pad) is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad.

20 In a preferred embodiment, the nozzle employed in the apparatus has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches. In this embodiment, the flexible restrictor preferably has an internal diameter ranging from about 0.002 to about 25 0.200 inches and a length of about 0.5 to about 12 feet. This embodiment of the apparatus is particularly preferred for applying the reagent in a continuous manner.

30 In another preferred embodiment, the nozzle employed in the apparatus has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches. In this embodiment, the flexible

-7-

restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet. This embodiment of the apparatus is particularly preferred for applying discrete amounts of the reagent to the test pad.

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In a preferred embodiment of the apparatus, the means for moving the test device is a conveyor.

10 In another preferred embodiment, the fluid delivery system comprises a plurality of nozzles and flexible restrictors. Preferably, the each of the plurality of nozzles and flexible restrictors is employed to apply a different concentration of the reagent thereby creating a gradient effect between each application of reagent.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a view of a continuous multi-nozzle coating system using a long flexible restrictor and a pressure delivery system.

20 Figure 2 is a view of a continuous multi-nozzle coating system using a long flexible restrictor and a positive displacement delivery system.

Figure 3 is a view of a discrete multi-nozzle coating system using a long flexible restrictor and a pressure delivery system.

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Figure 4 is a view of a discrete multi-nozzle coating system using a long flexible restrictor and a positive displacement delivery system.

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Figure 5 is a view of a nozzle system with brushes to dampen pump pulsation.

-8-

Figure 6 is a view of a slotted-head multiple nozzle.

Figure 7 is a view of a slotted-head multiple nozzle coating system using a long flexible restrictors and a pressure delivery system.

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Figure 8 is a view of a slotted-head multiple nozzle with a brush (felt pad) attached.

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DETAIL DESCRIPTION OF THE INVENTION

Test devices made using the methods and fluid delivery systems of the present invention to imbibe the reagent into the test pad use complete or partial prefabricated test devices. The test devices move either on a conveyor suitable for moving the test devices or as a continuous web. The amount of fluid required and the coverage is calculated so that the appropriate volume of reagent is dispensed on the device test pad.

For continuous deposition, the fluid delivery system dispenses a continuous stream of reagent. The length of the restrictor, the size of the nozzle, and the system pressure are selected using an iterative process to determine the amount of reagent delivered. The amount of fluid delivered is directly linked to the internal diameter (id) of the restrictor and nozzle and the length of each. For volumes in the range of less than one milliliter per minute, the nozzle id preferably ranges from about 0.005 to about 0.150 inches (about 0.0127 to about 0.381 cm) and has a length of about 0.2 to about 2.0 inches (about 0.51 to about 5.1 cm). To minimize any pulsation in the system, the restrictors preferably have an id of from 0.002 to 0.200 inches (about 0.011 to about 0.51 cm) and a length of about 0.5 to 12 feet (about 0.152 to about 3.66 m) depending on the temperature of the surrounding environment. Preferably, the restrictors are made from a flexible tubing, such as nylon or tygon. This creates a slight accumulation capacity in the system to damp out any pulsation. The nozzle size

-9-

for this example would have an id of 0.015 inches and a length of 6 inches. The composition of the nozzle is preferably PVC plastic, stainless steel or glass.

For discrete deposition, the invention generally dispenses a pre-determined amount of reagent, typically in the form of a drop. The length of the restrictor, the size of the nozzle and system pressure are selected using a similar iterative process as described above. However, to determine nozzle length and size, the amount to be delivered to an application site must be determined and the nozzles selected with a suitable end which can support formation of an adequate drop. The amount of fluid delivered is directly linked to the nozzle tip dimensions and shape, and to the internal diameter (id) of the restrictor and nozzle and the length of each. For volumes in the range of less than one milliliter per minute, the nozzle id is preferably less than or equal to 0.032 inches (0.0813 cm) and the length is preferably about 0.2 to about 2.0 inches (about 0.51 to about 5.1 cm). The restrictors preferably have an id of from 0.002 to about 0.200 inches (about 0.011 to about 0.51 cm) and a length of about 0.5 to about 12 feet (about 0.152 to about 3.66 m) depending on the temperature of the surrounding environment. To minimize any pulsation in the system, the restrictors are preferably made from a flexible tube such as nylon or tygon. This creates a slight accumulation capacity in the system to damp out any pulsation. The nozzle size for this example would have an id of 0.015 inches and a length of 6 inches. The composition of the nozzle is preferably PVC plastic, stainless steel or glass.

The opening of the nozzles employed in this invention may have any art-recognized shape, including round, oval or slit nozzles. The nozzle shape will typically be chosen based on the amount and the surface area of reagent desired on the test pad.

-10-

The fluid delivery system in either case typically further comprises a positive displacement system or pressure system. Examples of positive displacement systems include gravity feed systems and the like. Pressure systems include syringes, continuous flow pumps and the like. Pressure delivery systems for discrete reagent application require very fine pressure control and sharp on/off switching capabilities. A system such as those built by EFD corporation of Providence, RI (Model 1000DV) is suitable for use in this invention. Syringe pumps made by ISCO pump or Harvard Apparatus can also accommodate the deliver requirements for low volume discrete deliver applications.

Pumps create pulsations due to sticking of the seals or peristaltic action. If the flexible restrictors and nozzles are not sufficient to dampen these pulsation, a brush is preferably used on the underside to provide a path for the reagent to the membrane. The term brush refers to any object which serves to spread the reagent on the surface of the pad, including brushes with bristles and other spreading objects such as felt pads and the like.

In one of its embodiments, the present invention employs a plurality of nozzles and flexible restrictors. In this embodiment, the nozzles can be joined together to form a slotted-head. The various nozzles and flexible restrictors allow different concentrations of the reagent to be applied to the test pad. This creates a concentration gradient across the test pad. Alternatively, different reagents can be applied through each of the nozzles

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The reagent system used in this invention must be capable of detecting the presence of the analyte. In general, the analyte reacts with a specific oxidase or peroxidase enzyme and produces hydrogen peroxide. This strongly oxidative substance reacts with the indicator(s) present to produce a colored end product. Preferred oxidase enzymes for use in this invention include, but are not limited to, the following: glucose oxidase, cholesterol oxidase, uricase, alcohol oxidase,

-11-

aldehyde oxidase or glycerophosphate oxidase. Other oxidase or peroxidase enzymes will be readily evident to one who is skilled in the art.

The indicator chemistries which provide acceptable color generation when applied to the test pad may be chosen from 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) combined with 3-dimethylaminobenzoic acid (DMAB), MBTH combined with 3,5-dichloro-2-hydroxybenzene-sulfonic acid (DCHBS); 4-aminoantipyrene (4-AAP) and 5-oxo-1-(p-sulfophenyl)-2-pyrazoline-3-carboxylic acid (OPSP); 4-AAP and N-(m-tolyl)-diethanolamine (NDA); 2,2'-azino-di-(3-ethylbenzthiazoline)sulfonic acid (ABTS); 4-AAP and 4-methoxynaphthol; pyrogallol red (PGR); bromopyrogallol red (BPR); acid green 25 (AG); MBTH and 8-anilino-1-naphthalenesulfonate (ANS); or N-(3-sulfopropyl)aniline and MBTH; or other known and conventional dye system for different analytes. U.S. Patent No. 5,306,623 to Kiser et. al. discloses effective concentrations of a number of useful dye systems. Many other indicator reagent systems are known in the art and any of these may be used in this invention.

A preferred dye system is based on the sulfonated form of MBTH, 3-methyl-6-(M sulfonate)-benzothiazolinone-(2)-hydrazone (MBTH-S) where M is sodium, potassium, ammonium or other equivalent ion, but is preferably sodium. Sulfonation of MBTH to form MBTH-S is disclosed in U.S. Patent 4,101,381 to Klose. MBTH-S formed as a dye couple with DMAB, ANS or N-(3-sulfopropyl)aniline provides preferred indicator systems having stable color end points in a short period of time.

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The particular reagent system employed in this invention will determine, in part, the id and length of the nozzle and the restrictor employed. Typically, a smaller id and/or a longer length for the nozzle and/or the restrictor will be used when the reagent has a lower viscosity. Alternatively, the viscosity of the reagent can be modified or optimized for a particular delivery system by the addition to the reagent of well-known viscosity modifying agents and/or by

-12-

controlling the temperature of the reagent. In the latter case, the reagent can be warmed or cooled by heating or cooling the restrictors and/or the reagent reservoirs. For example, the restrictors and reagents reservoirs can be cooled to the desired temperature by immersing the restrictors and reservoirs in an ice bath
5 or by surrounding them with a refrigeration system. Similiarly, heating may be accomplished using a warm water bath or an oven. Depending on the reagent, cooling of the restrictors and reagent reservoirs also has the additional benefit of stabilizing the reagent system thereby preventing or reducing the decomposition of the reagent. Accordingly, the length of time the reagent is useable may be
10 significantly increased.

A further description of this invention may be obtained from the drawings.

15 Figure 1 is a view of a continuous multi-nozzle coating system using a long flexible restrictor 1 and a pressure pot delivery system 8 and nozzle 3. The reagent is dispensed from the nozzle and test pad 5 is impregnated.

20 Figure 2 is a view of a continuous multi-nozzle coating system using a long flexible restrictor 1 and a positive displacement delivery system 4 and nozzles 3. The reagent is dispensed from the nozzle and test pad 5 is impregnated.

25 Figure 3 is a view of a discrete multi-nozzle coating system using a long flexible restrictor 1 and a pressure delivery system 8 and nozzles 3. The reagent is dispensed from the nozzle and test pad 5 is impregnated.

Figure 4 is a view of a discrete multi-nozzle coating system using a long flexible restrictor 1 and a positive displacement delivery system 4 and nozzles 3.
30 The reagent is dispensed from the nozzle and test pad 5 is impregnated.

-13-

Figure 5 is a view of a nozzle system with nozzle 3 and brushes 7 to dampen pump pulsation and provide flow control. If the flexible restrictors and nozzles are not sufficient to dampen these pulsation, a brush is used on the underside to provide a path for the reagent to the membrane.

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Figure 6 is a view of a multiple slotted-head nozzle 8 having multiple openings 9 for delivery of multiple reagents or different concentrations of reagents to a test pad.

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Figure 7 is a view of a multiple slotted-head nozzle coating system using long flexible restrictors 1 and a pressure delivery system 4 and a multiple slotted-head nozzle 8. The reagent is dispensed from the nozzle to the test pad.

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Figure 8 is a view of a multiple slotted-head nozzle coating system using long flexible restrictors 1 and a pressure delivery system 4 and a multiple slotted-head nozzle 8 having a felt pad 10 attached. The reagent is dispensed from the nozzle through the felt pad to the test pad 5.

WHAT IS CLAIMED IS:

1. A method for applying a reagent to a test device comprising:
 - (a) providing a test device comprising a substrate and a test pad attached to the substrate;
 - (b) providing a fluid delivery system comprising a nozzle and a flexible restrictor attached to the nozzle for delivery of a reagent from the nozzle to the test pad;
 - (c) applying a reagent comprising an indicator system and an oxidase enzyme or a peroxidase enzyme in a predetermined amount and at a predetermined pressure through the nozzle and the flexible restrictor to the test pad.
- 10 2. The method of Claim 1 wherein the fluid delivery system further comprises a pressure delivery system.
- 15 3. The method of Claim 1 wherein the fluid delivery system further comprises a positive displacement system.
- 20 4. The method of Claim 1 wherein a brush is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad.
- 25 5. The method of Claim 1 wherein the reagent is applied continuously to the test pad.
- 30 6. The method of Claim 5 wherein the nozzle has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

-15-

7. The method of Claim 1 wherein the reagent is applied in a discrete amount to the test pad.

8. The method of Claim 7 wherein the nozzle has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

9. The method of Claim 1 wherein the oxidase enzyme is selected from the group consisting of glucose oxidase, cholesterol oxidase, uricase, alcohol oxidase, aldehyde oxidase and glycerophosphate oxidase.

10. The method of Claim 1 wherein the indicator system is selected from the group consisting of (a) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 3-dimethylaminobenzoic acid; (b) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 3,5-dichloro-2-hydroxybenzenesulfonic acid; (c) 4-aminoantipyrine and 5-oxo-1-(p-sulfophenyl)-2-pyrazoline-3-carboxylic acid; (d) 4-aminoantipyrine and N-(m-tolyl)-diethanolamine; (e) 4-aminoantipyrine and 4-methoxynaphthol; (f) 2,2'-azino-di-(3-ethylbenzthiazoline)sulfonic acid; (g) pyrogallol red; (h) bromopyrogallol red; (i) acid green 25; (j) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and 8-anilino-1-naphthalenesulfonate; (k) 3-methyl-2-benzothiazolinone hydrazone hydrochloride and N-(3-sulfopropyl)aniline; (l) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 3-dimethylaminobenzoic acid; (m) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and 8-anilino-1-naphthalenesulfonate; and (n) 3-methyl-6-(sulfonate)-benzothiazolinone-(2)-hydrazone sodium salt and N-(3-sulfopropyl)aniline.

30 11. The method of Claim 1 wherein the fluid delivery system comprises a plurality of nozzles and flexible restrictors.

-16-

12. The method of Claim 11 wherein each of the plurality of nozzles and flexible restrictors applies a different concentration of reagent to the test pad.

13. An apparatus for applying a reagent to a test device comprising a substrate and a test pad, said apparatus comprising:

- (a) a fluid delivery system comprising a nozzle and a flexible restrictor for delivery of the reagent to the test pad;
- (b) a support positioned under the fluid delivery system for supporting the test device; and
- (c) means for moving the test device under the fluid delivery system.

14. The apparatus of Claim 13 wherein the fluid delivery system further comprises a pressure delivery system.

15. The apparatus of Claim 13 wherein the fluid delivery system further comprises a positive displacement system.

16. The apparatus of Claim 13 wherein a brush is attached to the underside of the nozzle and the reagent is applied through the nozzle and then through the brush to the test pad.

17. The apparatus of Claim 13 wherein the nozzle has an internal diameter ranging from about 0.005 to about 0.150 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

18. The apparatus of Claim 13 wherein the nozzle has an internal diameter which is less than or equal to 0.032 inches and a length ranging from about 0.2 to about 2.0 inches, and the flexible restrictor has an internal diameter

-17-

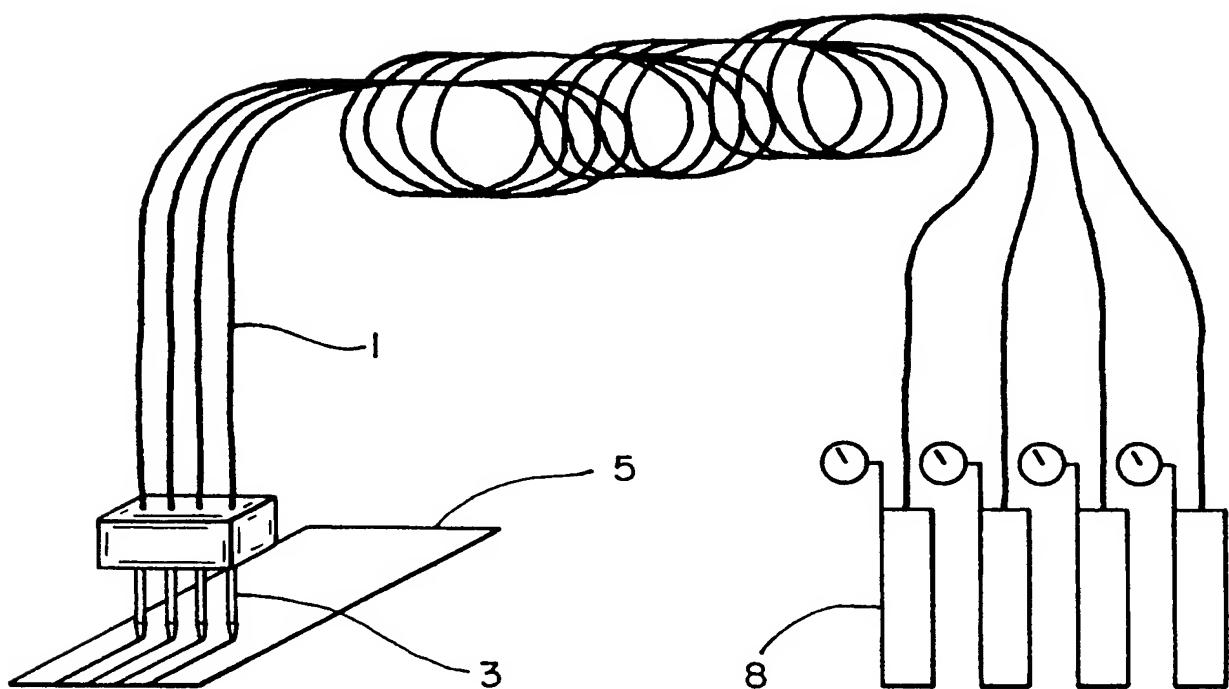
ranging from about 0.002 to about 0.200 inches and a length of about 0.5 to about 12 feet.

19. The apparatus of Claim 13 wherein the means for moving the test
5 device is a conveyor.

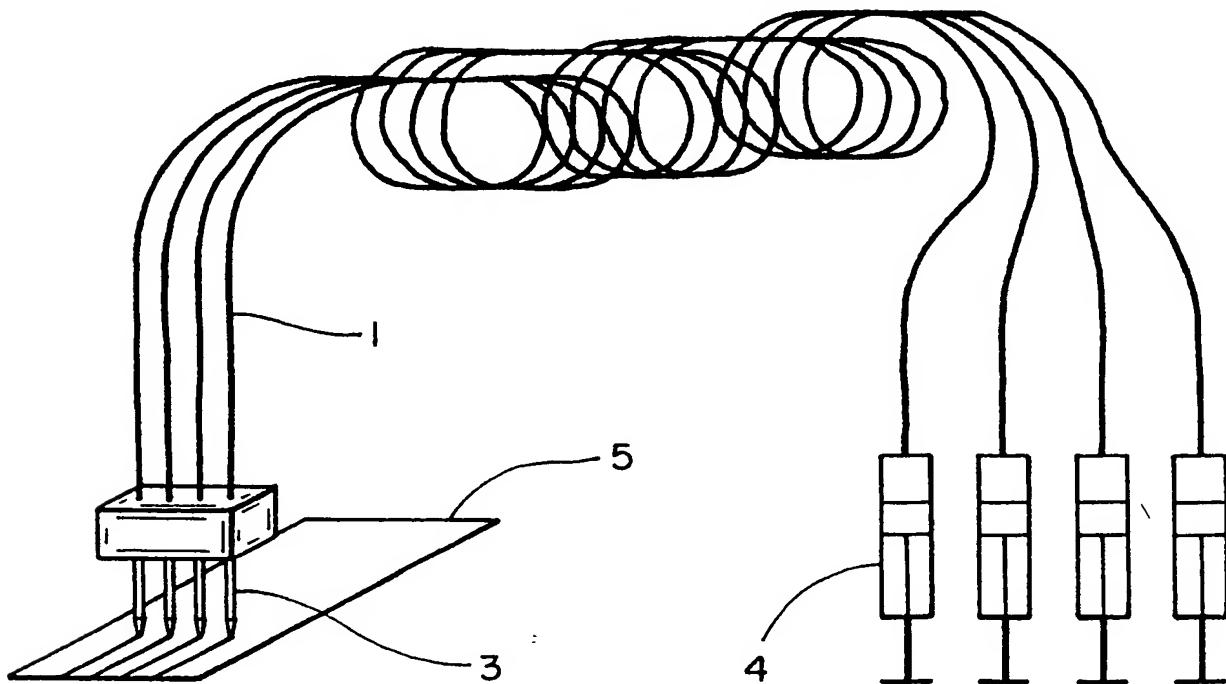
20. The apparatus of Claim 13 wherein the fluid delivery system
comprises a plurality of nozzles and flexible restrictors.

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1/4

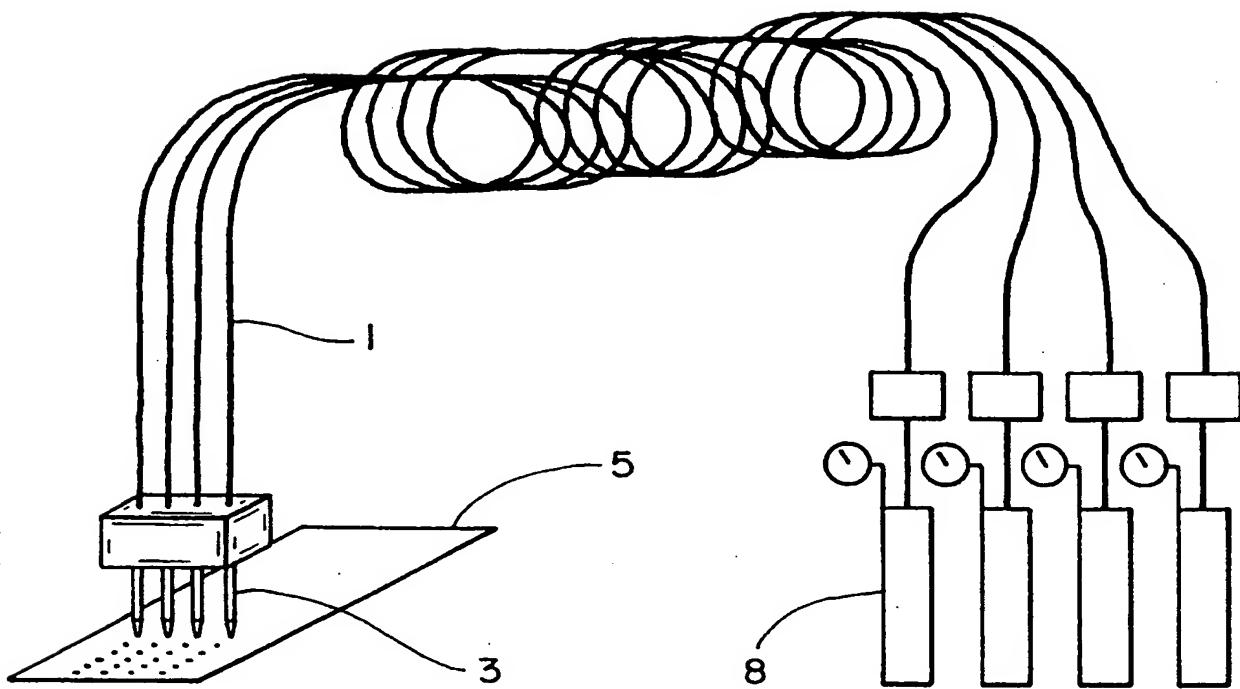


FIG_1

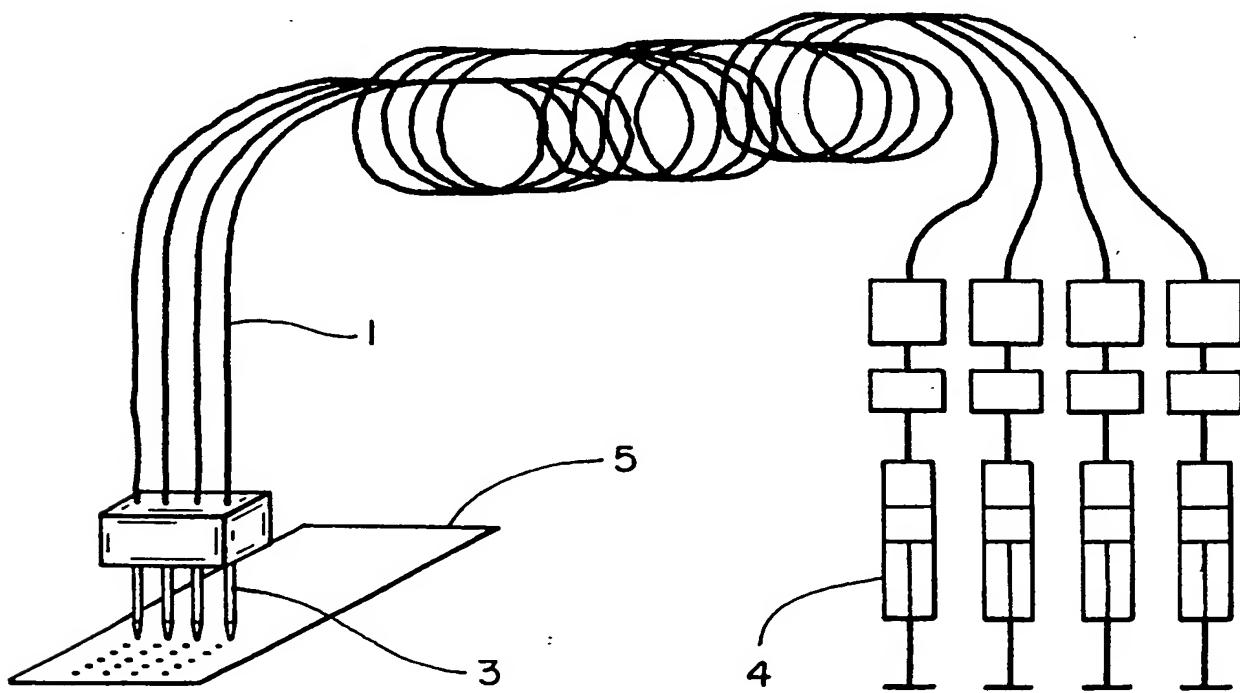


FIG_2

2/4

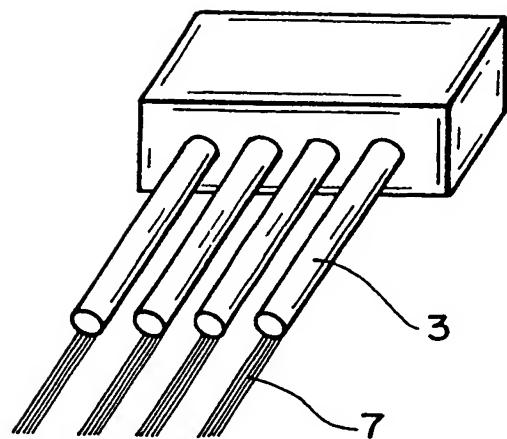


FIG_3

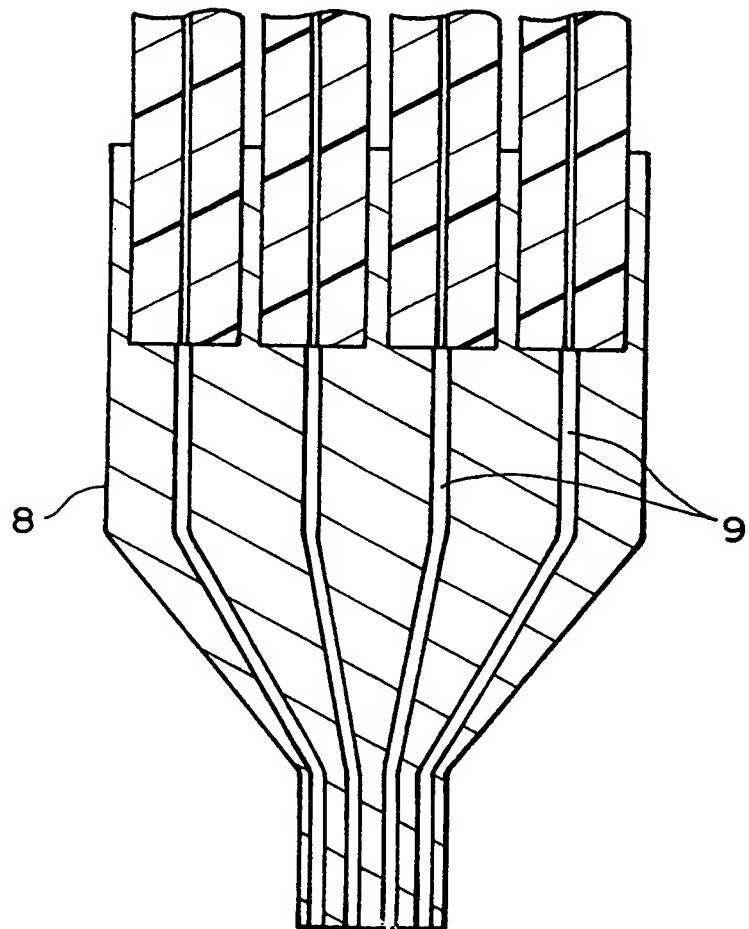


FIG_4

3/4



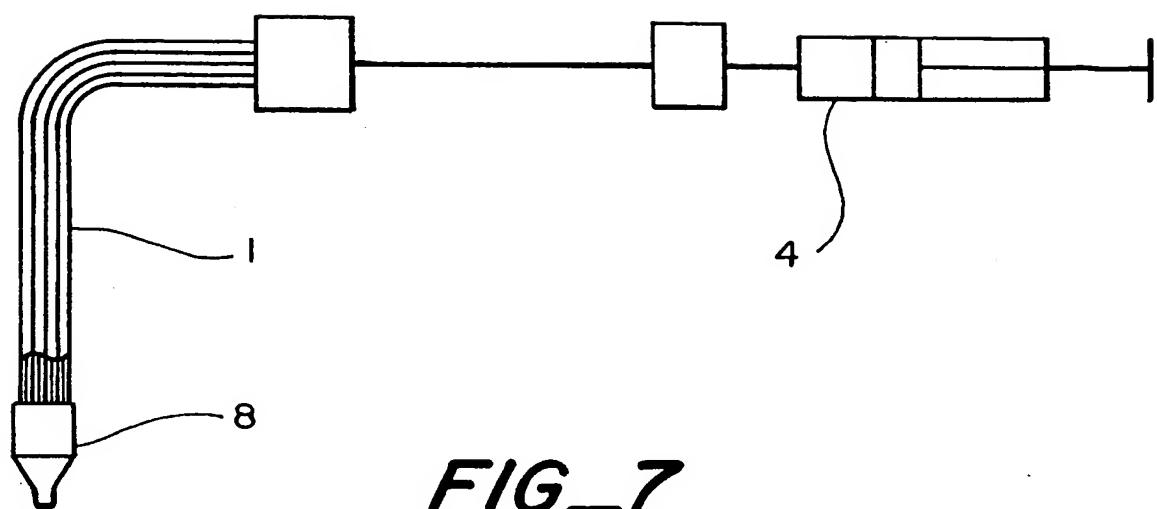
FIG_5



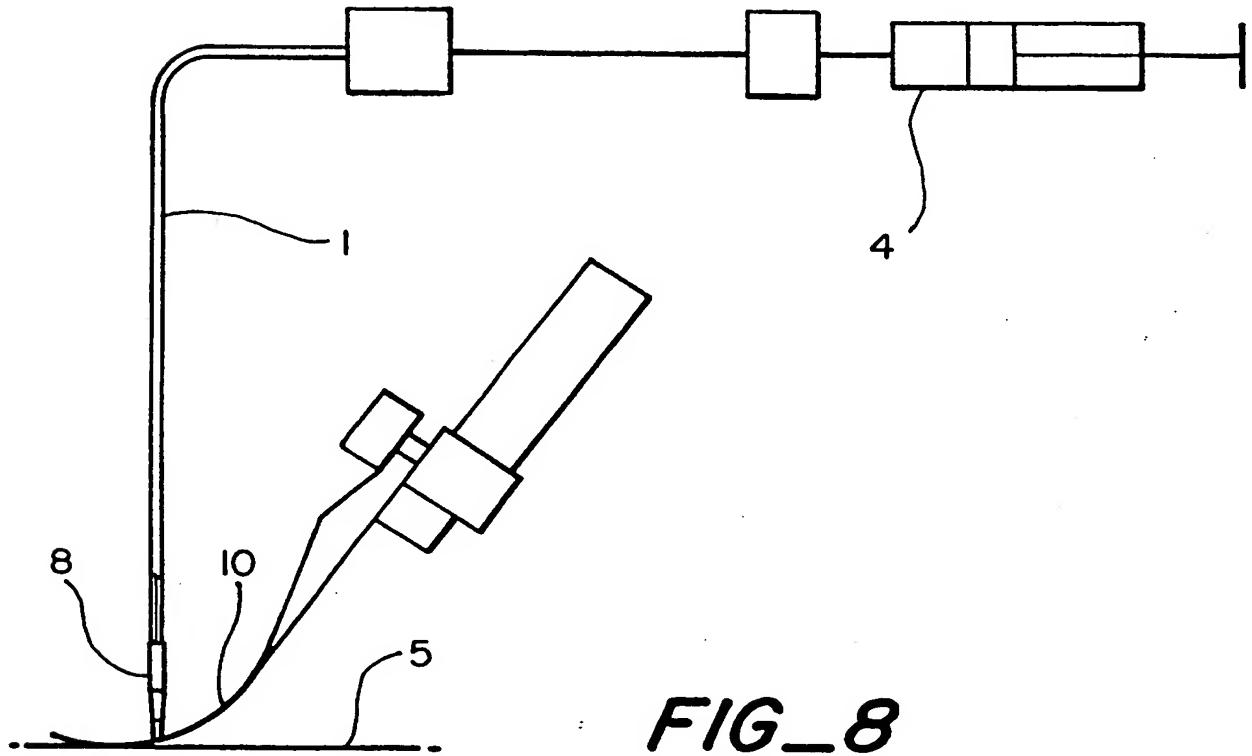
FIG_6

SUBSTITUTE SHEET (RULE 26)

4/4



FIG_7



FIG_8

INTERNATIONAL SEARCH REPORT

ional Application No

PCT/US 98/00477

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N33/52 C12Q1/26 //B05C5/02

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C12Q B05C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 130 085 A (HEWITT RAYMOND) 19 December 1978 see column 1, line 7 - column 1, line 11 see column 2, line 63 - column 3, line 17 see column 3, line 31 - column 3, line 67 see column 4, line 32 - column 4, line 62 see column 5, line 1 - column 5, line 50 see column 6, line 56 - column 7, line 24 see figures 1-3 --- -/-/	1,2,5,7, 9,11-14, 20

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- "E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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